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VOLUME 61 NUMBER 2

# ARCHIVES
OF
# DERMATOLOGY AND SYPHILOLOGY

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FEBRUARY 1950

PUBLISHED MONTHLY BY AMERICAN MEDICAL ASSOCIATION, 535 NORTH DEARBORN STREET, CHICAGO 10, ILLINOIS. ANNUAL SUBSCRIPTION, $12.00

Entered as Second Class Matter Oct. 30, 1917, at the Postoffice at Chicago, Under the Act of Congress of March 3, 1879

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## CONTENTS OF PREVIOUS NUMBER

### JANUARY 1950. NUMBER 1


Cutaneous Changes in Lupus Erythematosus: Histopathologic Aspects, with Special Reference to Vascular Changes. William G. McCreight, M.D., and Hamilton Montgomery, M.D., Rochester, Minn.

Lymphosarcoma Treated with Nitrogen Mustard: Report of a Case. S. E. Sweitzer, M.D., and H. A. Cumming, M.D., Minneapolis, and G. D. McAfee, M.D., Cincinnati.

Chronic Lupus Erythematosus: Report of an Unusual Case with Concomitant Subcutaneous Edematous Nodes and Swellings; Historical Review. J. L. Grund, M.D., Boston.

A Theory of the Pathogenesis of Ordinary Human Baldness. Thomas S. Szasz, M.D., and Alan M. Robertson, M.D., Chicago.

Penicillin in the Treatment of Experimental Syphilis of Rabbits. John A. Kolmer, M.D., with the Technical Assistance of Anna M. Rule, Philadelphia.

V. The Synergistic or Additive Activity of Penicillin Injected Intramuscularly with Sodium Iodide Administered Orally and Intravenously.

VI. The Synergistic or Additive Activity of Penicillin Injected Intramuscularly and Tryparsamide Administered Intravenously.

Sjögren's Syndrome. Howard T. Behrman, M.D., and K. K. Lee, M.D., New York.

Arteriosclerosis Obliterans as a Cause of Ulcers of the Leg. Seymour I. Shapiro, M.D., and Ruben Nomland, M.D., Iowa City.

Parakeratosis Scutularis (Ostracea). Bethel Solomons Jr., M.D., M.R.C.P.I., Dublin, Eire.

Investigation of Fungi in Hanging Drop Cultures: Preliminary Report. A. A. Zimerinov, and S. M. Rafalovich, Kiev, U.S.S.R.

Clinical Notes:

Sebaceous Nevus and Nevus Syringadenomatosus Papilliferus Occurring as a Mixed Form: Report of a Case. Morris D. Marcus, M.D., St. Louis, and Wilfred E. Wooldridge, M.D., Springfield, Mo.

Granuloma Papulonecroticum or Papulonecrotic Tuberculid: Report of a Case. William Guy Jr., M.D., Pittsburgh.

Dermatitis Caused by Garlic. A. J. Edelstein, M.D., Johnstown, Pa.

Dermatitis from Nylon® Hair Nets. C. Russell Anderson, M.D., Beverly Hills, Calif.

Simple Clinical Color Photography. John van de Erve Jr., M.D., Charleston, S. C.

Comparison of Finger Nails in Negroes and White Persons. Robert H. Harris, M.D., Long Beach, Calif.

Restrictions Regarding Use of Diathermy Apparatus. Anthony C. Cipollaro, M.D., New York.

Pityriasis Rosea Accompanied with Bell's Palsy. Louis G. Jekel, M.D., Phoenix, Ariz.

Dermatitis Accentuated by Gauze: Report of a Case. Lester Hollander, M.D., Pittsburgh.

Compound Benzoin Tincture in Treatment of Vesiculobullous Lesions of Mucous Membranes. Henry Harris Perlman, M.D., Philadelphia.

Lichen Planus Hypertrophicus: Possible Clue to Etiology. Charles C. Dennie, M.D., and Francis P. Coombs, M.D., Kansas City, Mo.

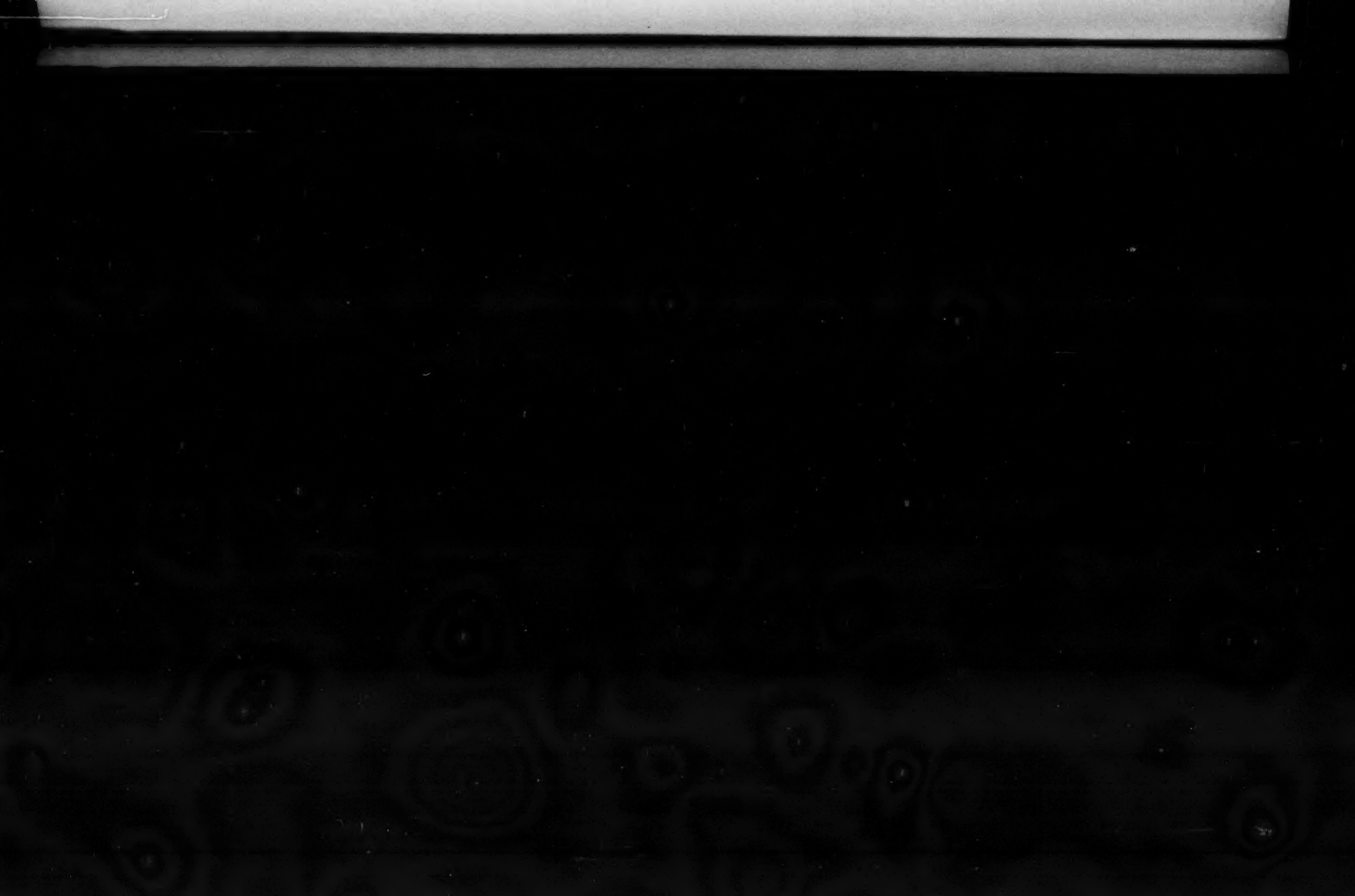
Ringworm of the Scalp of an Adult: Report of a Case. Victor R. Hirschmann, M.D., and Sidney Olansky, M.D., Durham, N. C.

Society Transactions:

Bronx Dermatological Society.
Brooklyn Dermatological Society.
Cleveland Dermatological Society.
Los Angeles Dermatological Society.
New England Dermatological Society.
Philadelphia Dermatological Society.
San Francisco Dermatological Society.

News and Comment.

Book Reviews.



Archives of Dermatology and Syphilology

VOLUME 61 FEBRUARY 1950 NUMBER 2

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# Editorial

Criticism of the Society Transactions has recently come to our attention. The comments were directed to the scarcity of the society reports, delay in their publication, the editing and deletion of some discussions and the omitting of some of the cases presented from the published reports. We are pleased to learn of these reactions and to know that so many read and enjoy this feature of the ARCHIVES.

The policy both past and future in regard to the publication of society meeting reports has been influenced by many factors: to wit, a long printers' strike, lack of paper, insufficient editorial help and a manuscript file which contained at one time two hundred and fifty papers and few reports of society meetings. These problems have been overcome, but new ones have arisen. Today there are many more dermatologists in this country than before the war and many more dermatologic societies, so that more men are saying more things at more meetings, with the result that a society report which formerly consisted of twenty pages has now grown to fifty or more pages. Accordingly, enough pages of meeting reports are received each month to fill an entire issue of the ARCHIVES.

Unfortunately, not all these reports warrant printing; some are inane, and others are irrelevant and convey no new or old thoughts and serve no purpose. Many are unusable as received; some are quite good, and but few are excellent. Our course therefore has been to edit and delete the unessential parts of the reports and to publish as many as possible. The Editorial Board is not obligated to publish every manuscript submitted to it, and likewise it is not obligated to publish all details of all dermatologic meetings, even though it would like to. Accordingly, it will be necessary to continue to edit and delete so that the function of the Transactions will continue to be that of serving all subscribers as a valuable and instructive form of literature, a means for an exchange of ideas and the opportunity to express an opinion publicly.

The secretaries of the dermatologic societies could be of material help if they or a committee, at the close of the meeting, would cull out the cases and discussions that were not instructive. Discussions that are casual or inconsequential, unrelated laboratory reports and insignificant

historical data can well be omitted. The rare case, if not discussed, can be reported by title with the name of the presenter but without description. Discussions that are thoughtful, informative and clearly expressed are sought—in fact, fewer cases, better presented and more instructively discussed, would improve the caliber of the Transactions.

For the future it is planned to devote more space to Transactions and to publish them as soon as possible following their receipt, but reports that are received from the society secretaries a year or more after the meeting are already obsolete.

THE EDITOR.

# APPRAISAL OF OBJECTIVES AND FUNCTIONS OF THE AMERICAN DERMATOLOGICAL ASSOCIATION

**Presidential Address**

HARRY R. FOERSTER, M.D.
MILWAUKEE

IN A MEDICAL world that has been continuously changing because of the impact of social, economic and educational forces, the American Dermatological Association has held fast, for three quarters of a century, to the traditional concepts of its founders. This adherence to tradition has made our Association a conservative and venerable institution. In the light of rapidly changing conditions, it now appears timely to appraise our objectives and functions as they have beeen operating under both the stimulus and the inhibitions of tradition and to determine on a future course best suited to further our aims in a social structure that is becoming increasingly competitive.

In our present era the practice of medicine has become the concern of the public and research in medicine has become the project of wealthy foundations, well organized commercial organizations and governmental agencies. Lay groups, as represented by large national industries, labor unions, insurance carriers and political bodies, up to and including the President of the United States, have assumed certain interests and responsibilities for the public health, or intend to assume them.

As individuals and as an organization we cannot safely ignore these social and economic forces by confining our energies and activities solely to scientific and educational matters. Our primary objective should still be "to promote the study of dermatology in all its relations," in accordance with our traditions and with the highest ethical, moral and scientific standards. We should, however, also concern ourselves with meeting, in a practical way, the impact of the trends of today as they affect the practice of dermatology and syphilology and concern ourselves particularly with equipping our younger colleagues and students to meet these changing conditions.

I believe that we as an association, through group and committee action, should address ourselves more directly and more actively than

Read at the Sixty-Ninth Annual Meeting of the American Dermatological Association, Inc., at Hot Springs, Va., May 25, 1949.

we have in the past to all educational and social problems that concern dermatology. We must constantly move forward, if only to keep our place, and must assume new obligations if we are to lead rather than to follow in our field.

Among problems that merit our consideration are the initiation of cooperative efforts with other national dermatologic organizations and with other specialty groups for the study of matters of common interest, and also the formulation and adoption of minimum educational and teaching standards as they may apply not only to the student but also to the teacher, in both graduate and undergraduate fields, the projection of dermatologic research on a wider and larger scale than we are capable of achieving alone and the consideration of plans for publicity to advance dermatology and widen its field of activities and influence. In so doing I believe we would not be departing from but would be expanding the original concepts in order to keep pace with changing conditions.

A program for consideration of anything of this nature will require much more time for executive sessions than has been accorded them in the past. It will necessitate a prearranged executive program or agenda somewhat in balance with the scientific program. It will also call for more active committee work, or functioning of the directors, throughout the year instead of on a four day a year basis and the allocation of funds for each project.

I suggest that executive sessions be scheduled separately from scientific sessions for an adequate trial period and that each year one or two half-day sessions be designated for the consideration of matters of this nature, preferably selected for presentation and discussion by the board of directors.

## COOPERATIVE ACTIVITIES

In the days when the concerns of a specialty were its own affair a lack of cooperative spirit and incentive resulted in the dissolution of the American Congress of Physicians and Surgeons. Now, with a tremendous increase in specialization and with new social and economic problems confronting us, it appears desirable for the various specialty groups to be reunited for study and action on matters of mutual interest.

Twenty-seven years ago Ormsby recorded 300 dermatologists, or 1 to every 500 practicing physicians, in the United States. Fifteen years ago Senear recorded an 18 per cent increase in the number of all physicians in the preceding fifteen years, with the increase in specialists at 118 per cent and of dermatologists at 140 per cent. Two years ago O'Leary reported 363 graduate students in dermatology.

Last July there were 911 certified specialists in dermatology and syphilology. At that time the American Boards had certified 29,000 as specialists among 160,000 practicing physicians, a ratio of 1 to 5.5. No voluntary plan devised by medical groups and no compulsory political plan for medical care has given serious consideration to the significance and importance of this growth of specialism. It indicates progress in medical knowledge and vastly improved medical care, and yet specialists have been placed on the defensive.

Revival of the Congress, therefore, merits consideration for the purpose of coordinating the activities of the specialties and planning for their proper participation in the changing order of medical practice. An alternative and perhaps more feasible procedure would be the formation of a skeletonized organization of the directors or elected representatives of all member associations of the former Congress or of the various present associations and academies. Such a group could meet annually in executive session to consider problems of mutual interest in the educational, economic and political fields. They could work in liaison with the existing Advisory Board for Medical Specialties when their problems overlapped.

The time is opportune also for organizing our own national dermatologic societies into a cohesive group, working together for our common dermatologic interests in wider fields than those that have called for our participation in the past. For the latter purpose I would suggest a committee composed of the senior or retiring director of each of our three dermatologic groups, appointed on a staggered service basis so that there would be developed a continuously functioning body. Such a committee could meet throughout the year, in accordance with need, and report annually on its findings and recommendations to the respective parent bodies.

## MEMBERSHIP

A decision on future objectives and their realization will be dependent in large measure on the nature of our membership.

Rigid qualifications for membership have given this Association its character, stability and prestige, but at times, because of acceleration of specialization, as after each of the two world wars, qualified candidates have exceeded the numerical limitations. How large an influx of new members may the membership committee safely advocate without impairing certain traditional functions of our meetings? Shall we revise the qualifications or restrict the field?

It has been suggested that the Association limit itself to pedagogy and direct its activities to that field. Without having consciously arrived

at that objective we are essentially an organization of teachers of dermatology. A survey of the present membership of 145 reveals 119 with professorial rank. We have 19 professors emeritus, 2 retired professors, 46 professors, 30 associate professors, 22 assistant professors and 10 members in lesser teaching catagories. Only 16 members are not engaged in teaching and these largely because of locations not providing opportunites for teaching. These last-mentioned men are valued members who have contributed to teaching by their writings and program participations.

This Association was organized to furnish leadership in the advancement of dermatology. If we restrict our selection of members to those qualified for leadership on the basis of their established records in teaching, research or productive activity and scrutinize such records carefully we need not adhere to numerical limitations or worry about the Association's becoming unwieldy because of size. A rigid adherence to such qualifications will maintain the stability, character and effectiveness of the Association regardless of its size. I do not believe that a rigid adherence to a numerical limitation has ever met an issue or solved a problem.

## OTHER DERMATOLOGIC ORGANIZATIONS

A discussion of selective membership brings up the subject of our relations with our sister organizations in dermatology.

The American Academy of Dermatology and Syphilology was organized in 1938 by several members of this Association on the initiative and action of Paul O'Leary and in recognition of the need of a society for the specialists certified by the American Board. Its chief purpose has been the continuation of the teaching of dermatologists and syphilologists and the promotion of dermatologic interests through group association of all certified specialists.

The American Society for Investigative Dermatology was organized in 1938, also on the initiative of a member of this Association, Marion Sulzberger. The purpose of the society is to coordinate the activities of all men interested and active in investigative work in our field without regard to their qualifications as dermatologists and to obtain an additional outlet for the publication of papers on research.

The Section on Dermatology and Syphilology of the American Medical Association has never been an elective or selective organization and owes its identity as a group to component membership in that Association. It has served as a proving ground and provided a forum for the younger dermatologists.

These three organizations have always enjoyed the leadership and guidance of members of the American Dermatological Association though our Association did not promote their establishment. They are not rival or competitive organizations since their functions and objectives are wholly different.

It must be apparent that some of the traditional activities to which our Association has devoted itself for seventy-four years now are being shared by its fellow organizations, resulting in some duplication of effort and overlapping of activities. It should, therefore, be possible and it may be advisable for us to consider discontinuing certain of our functional activities. We may advantageously consider ways and means of revising our program so that the Association may confine itself most effectively to those projects and objectives that fall peculiarly into our sphere of activity and dominance, such as guiding and directing teaching and research, establishing policies for dermatologic activities and maintaining for our specialties their proper place in the field of medicine.

## TEACHING

At the time of our founding there were but twelve medical schools in this country in which instruction was given in diseases of the skin. The entire teaching capacity was represented by 3 professors, 2 clinical professors and 2 instructors.

The subject of teaching has been analyzed from time to time in our presidential addresses, but I believe I am correct in stating that the Association has never taken concerted action outside of its meeting rooms to project its convictions on the subject and to urge their adoption. It has taken the medical experiences of two world wars to convince, at least in part, the military services and the medical profession at large of the prevalence and the disabling and at times serious character of diseases of the skin and the importance of adequate and proper teaching of dermatology to undergraduate students. In spite of this background, the teaching of dermatology in many class A schools is still inadequate and astonishingly variable and largely out of balance. At the present time some top schools devote as little as five hours of curriculum time to the didactic teaching of dermatology; some do not have organized clinical teaching; some do not teach cutaneous syphilis in the course on dermatology, and some do not teach it in any course. The medical graduate who enters practice is, in many instances, very poorly equipped with a practical knowledge of diseases of the skin, for which he has a real need, though he is equipped with much special knowledge in some other fields, for which he has no real use or opportunity of application.

In those institutions where the undergraduate receives adequate teaching of high quality the ground work of personal effort of a leading member of this Association, past or present, is or has been invariably evident.

In our addresses concerned with teaching I have failed to observe references to necessary qualifications for the teachers. To advocate certain standards of teaching, as delineated by minimum hours of didactic and clinical teaching, without specifying the nature and quality of the teaching and the qualifications of the teacher, is evading an important issue.

I believe this Association should take official action in advocating the adoption of certain minimum requirements for professorships and for other teaching assignments to elevate the standards of teaching, as well as curricular requirements, just as in the past it has advocated, initiated and supported the certification of dermatologists to elevate the standards of practice.

Graduate teaching of dermatology in this country is of high caliber, but it in turn should be subjected to careful scrutiny by a committee of this Association and discussed by the members on a prearranged program. The preceptor phase of this teaching is wide open to serious criticism. The selection of graduate students has not been properly controlled or directed, and no doubt the whole program would benefit from critical analysis by this Association.

### PERMANENT FUND AND RESEARCH AID

When the constitution and by-laws were revised in 1927 great expectations accompanied the setting-up of a permanent fund and the formation of a research aid committee. It was hoped that members would provide sizable contributions for its growth, that outside sources of aid would be successfully solicited and that research activities of a fruitful nature would be set in motion. Unfortunately these hopes have not been realized. Small sums have been allocated for research projects in the past, but I do not believe that a real objective has been gained. The interest from the fund, available for research, amounts to only approximately $600 a year.

Contributing funds to already established and functioning foundations and projects merits consideration. The research aid committee can determine on likely or desirable fields for research and where they can be undertaken most effectively. Our secretary has suggested, as a project for the committee, that certain sums be appropriated annually for the awarding of prizes for laudable research work.

The words "publicity" and "promotion" have an undesirable connotation when used in connection with medicine. However, progress in special fields, as regards both practice and research, has advanced most where lay interests have been aroused. Publicity and promotional activities have been effective in raising large private funds to combat poliomyelitis, cancer and heart disease. Diseases of the skin do not have the same dramatic appeal, but there are highly important and fertile fields for dermatologic research. Money available from our permanent fund might well be used by the research aid committee to gather statistical and other pertinent information to show what needs to be done as the basis for soliciting and popularizing aid from larger funds or foundations.

## PUBLICATIONS

The Association has always recognized the importance of publishing its scientific papers and initiated this procedure in 1880. Various mediums have been employed during the years because of dissatisfaction with delays in publication, editing problems and expenses involved and for other reasons. Our present procedure is the best we have attained, and the editors deserve high commendation. However, early and combined publication of all Association papers in several supplementary volumes to the ARCHIVES, if feasible, would stimulate original contributions to the program. The added cost could be met by popular subscription or by increasing the price of the ARCHIVES. There would still be enough other material available for the regular monthly issues. An alternative consideration would be authorization by the American Medical Association for the allocation of some research papers to *The Journal of Investigative Dermatology*. Early publication of some articles of more general interest, particularly lengthy essays or monographs, could probably be provided by some medium of wide circulation other than the present authorized channels.

The purpose of a presessional volume, as undertaken in 1929, is fundamentally sound, but the expense involved and other considerations led to its abandonment. A variant to be considered is the publication in the program of more detailed abstracts of papers than it has been our custom to include or the separate electrotyping of detailed abstracts prior to the meeting. It is desirable that something be done along these lines to attract original and timely contributions of merit for the program and to encourage carefully considered discussions.

Some of these proposals may seem to be impractical or unnecessary extensions of our interests and activities into a field far removed from the purposes of this Association. In regard to matters correlated to our

past activities, you may hold to the belief that our Association will still function best and maintain its prestige by continuing along the well worn path of tradition, aloof from ventures in new fields. It is my belief that to progress we must undertake new objectives and project our activities over new horizons.

I therefore leave these thoughts for your consideration and thank you again for the privilege of expressing them and for the honor of presiding at this meeting, which I hope you will all find profitable and enjoyable.

208 East Wisconsin Avenue.

# TREATMENT OF SYPHILIS WITH AUREOMYCIN ADMINISTERED BY MOUTH

ROBERT R. KIERLAND, M.D.
WALLACE E. HERRELL, M.D.
AND
PAUL A. O'LEARY, M.D.
ROCHESTER, MINN.

WHAT MIGHT be called the "antibiotic era" of syphilotherapy began with the introduction of penicillin in the treatment of syphilis. Naturally, therefore, antibiotics developed since the introduction of penicillin also have been examined for their possible value in the treatment of syphilis. The new antibiotic aureomycin appears to have a wide range of antibacterial activity. The present report is concerned with an expansion of our previously reported investigations on its oral use in the treatment of syphilis.

It was evident from the report by Heilman [1] that aureomycin possesses antispirochetal activity which is greater than that of penicillin against experimental infectious relapsing fever and leptospirosis icterohaemorrhagica. His observations led us to administer aureomycin orally to patients with early infectious syphilis [2] and to patients with late cutaneous syphilis and neurosyphilis [3]. The results obtained showed that aureomycin has definite antisyphilitic activity when administered by the oral route; it produces rapid healing of cutaneous lesions and brings serologic negativity to patients with early syphilis.

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Supplies of aureomycin were provided by Lederle Laboratories Division, American Cyanamid Company.

Read at the Sixty-Ninth Annual Meeting of the American Dermatological Association, Inc., Hot Springs, Va., May 27, 1949.

From the Section on Dermatology and Syphilology (Dr. Kierland and Dr. O'Leary) and the Division of Medicine (Dr. Herrell), Mayo Clinic.

1. Heilman, F. R.: Aureomycin in the Treatment of Experimental Relapsing Fever and Leptospirosis Icterohaemorrhagica (Weil's Disease), Proc. Staff Meet., Mayo Clin. **23**:567-573 (Dec. 8) 1948.

2. O'Leary, P. A.; Kierland, R. R., and Herrell, W. E.: The Oral Administration of Aureomycin (Duomycin) and Its Effect on Treponema Pallidum in Man, Proc. Staff Meet., Mayo Clin. **23**:574-578 (Dec. 8) 1948.

3. O'Leary, P. A.; Kierland, R. R., and Herrell, W. E.: Oral Aureomycin in the Treatment of Late Cutaneous Syphilis, Proc. Staff Meet., Mayo Clin. **24**: 302-306 (May 25) 1949.

Others also have shown that aureomycin is effective in bringing about resolution of the early infectious lesions of syphilis [4].

We wish to present the results obtained by the oral administration of aureomycin for a sampling of 7 patients with early infective syphilis, late cutaneous lesions of syphilis or neurosyphilis. Treatment of another patient was started but was discontinued.

### EARLY SYPHILIS

Two patients with dark field–positive primary lesions of syphilis were treated with aureomycin given orally. In both, results of the dark field examinations became negative rapidly, the lesions healed and the serologic reactions for syphilis became negative. There had been no clinical or serologic evidence of relapse to the time of the present report.

CASE 1.—A white man 38 years of age came to the Mayo Clinic because of a scrotal ulcer of two months' duration. In the week prior to admission, an eruption

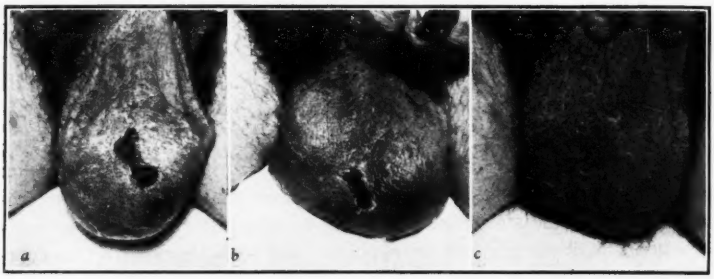


Fig. 1 (case 1).—Early lesions. (*a*) Dark field–positive primary lesion of syphilis before oral treatment with aureomycin. Note peripheral infiltration and induration. (*b*) Same lesion eleven days after beginning of treatment. Note healing and the resolution of the infiltration and induration. (*c*) Same lesion forty-two days after beginning of treatment, showing complete healing of primary lesion.

of the lower lip, palms and soles and left axilla had developed, associated with headache, general malaise and sore throat. In addition to the superficial ulceration, measuring 4 cm. in diameter, on the anterior surface of the scrotum (fig. 1*a*), there were superficial erosions of the mucous membrane of the lower lip, erythematous papules on the palms and soles and a faint maculopapular eruption on the trunk. General examination otherwise was noncontributory.

Dark field examinations revealed the presence of Treponema pallidum, and serologic tests of the blood for syphilis gave positive reactions.

The patient was hospitalized on the day of admission, and treatment with aureomycin was begun. A dose of 400 mg. was given orally every four hours. On the fourth hospital day the dose was increased to 500 mg. every four hours. From

4. Irgang, S., and Alexander, E. R.: Treatment of Early Syphilis with Aureomycin: Preliminary Report, Harlem Hosp. Bull. **1**:91-98 (Dec.) 1948. Taggart, S. R., and Olansky, S.: Personal communication to the authors.

the sixth through the seventh day the patient received 750 mg. every four hours, and from then on throughout the rest of his hospital stay 500 mg. was administered every four hours. The total dose of aureomycin given was 44.2 Gm.

Results of dark field examinations became negative sixty hours after treatment was begun and remained negative thereafter. A febrile Herxheimer reaction was noted twenty-four hours after treatment was begun. Sixty hours after treatment was begun the roseola was still present but the primary lesion had begun to heal.

TABLE 1.—*Results of Serologic Tests for Syphilis in Case 1 After Treatment Was Begun*

| | Kline | Kahn | Hinton | Wassermann (Kolmer) | Quantitative Titer, Kahn Units |
|---|---|---|---|---|---|
| Before treatment | ++++ | ++++ | + | +++ | 256 |
| Time after beginning of treatment, days | | | | | |
| 12 | ++++ | ++++ | + | +++ | 128 |
| 40 | ++++ | ++++ | + | +++ | 32 |
| 72 | + | + | ± | — | ... |
| 103 | — | — | — | — | ... |
| 136 | — | — | — | — | ... |
| 172 | — | — | — | — | ... |

TABLE 2.—*Serologic Reactions in Case 2 After Treatment Was Begun*

| | Kline | Kahn | Hinton | Wassermann (Kolmer) | Quantitative Titer, Kahn Units |
|---|---|---|---|---|---|
| Before treatment | — | — | + | — | ... |
| Time after beginning of treatment, days | | | | | |
| 7 | +++ | ++++ | + | ++++ | 8 |
| 14 | ± | +++ | + | ++++ | 3 |
| 23 | ± | — | + | +++ | |
| 38 | — | — | ± | — | ... |
| 54 | — | — | ± | — | ... |
| 66 | — | — | — | ± | ... |
| 95 | — | — | — | — | ... |
| 129 | — | — | — | — | ... |
| 173 | — | — | — | — | ... |
| 296 | — | — | — | — | ... |

At ninety-six hours the roseola had faded, the mucous patches had healed and the primary lesion was healing rapidly. Figure 1 (*b* and *c*) illustrates the rapid healing of the primary lesion. The patient was dismissed sixteen days after treatment was begun. All lesions had healed. There was, however, still residual induration at the site of the chancre. Results of examinations of the cerebrospinal fluid were negative for syphilis in this case.

Reactions to serologic tests of the blood for syphilis at varying intervals from the beginning of treatment are given in table 1.

CASE 2.—A white man aged 24 years came to the clinic because of an ulcerated penile lesion of one week's duration. The ulcer measured 1 cm. in diameter and was located on the anterior surface of the penile shaft. There were no other objective evidences of syphilis. The results of the dark field examination for T. pallidum were positive.

Aureomycin was given orally in doses of 750 mg. every four hours for fifteen days, for a total dose of 67.5 Gm. Twelve hours after the beginning of therapy the results of the dark field examination were positive, but at sixteen hours and thereafter they were negative. Four days after the beginning of treatment the primary lesion was 50 per cent healed. At the end of the treatment period the primary lesion had completely healed.

Serologic reactions from the time treatment was begun are reported in table 2.

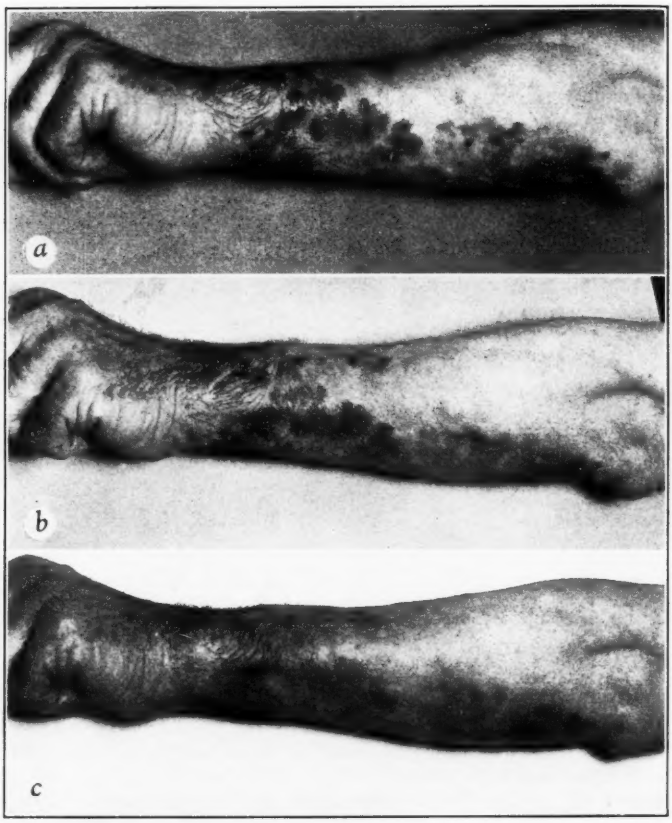


Fig. 2 (case 3).—Noduloulcerative syphiloderm on left forearm, of ten years' duration. (*a*) Before treatment. (*b*) Same lesion ten days after oral administration of aureomycin was begun. (*c*) Same lesion sixty-nine days after therapy was begun and fifty-one days after cessation of treatment. Note absence of inflammatory activity.

### LATE CUTANEOUS SYPHILIS

Two patients with long-standing, previously unrecognized late noduloulcerative cutaneous syphilis were treated with aureomycin administered orally. The results were excellent in that the cutaneous lesions

quickly disappeared and healing progressed rapidly. The serologic patterns had shown no change during the short period of observation up to the time of the present report.

CASE 3.—A white man 64 years of age came to the clinic with complaints of poor vision and diabetes mellitus. On physical examination an eruption of ten years' duration involving the left forearm, groin and right knee was noted, for which the patient was referred for dermatologic study. The characteristics of a late superficial ulceronodular syphiloderm were recognized (figs. 2*a* and 3*a*). In addition, physical examination revealed aortic regurgitation which was felt to be syphilitic in type. The Kline, Kahn, Hinton and Kolmer serologic reactions for syphilis were positive, and the Kahn quantitative titer measured 128 units. The cerebrospinal fluid was normal.

The patient was given 250 mg. of aureomycin orally every six hours for three days. Then the dose was increased to 500 mg. every six hours for three days.

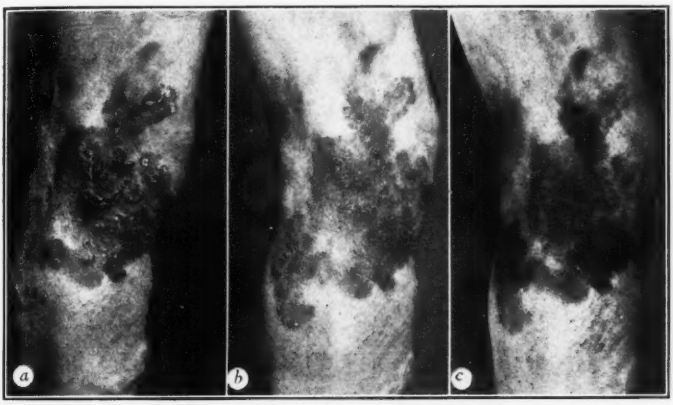

Fig. 3 (case 3).—Noduloulcerative syphiloderm of right knee. (*a*) Before treatment. (*b*) Same lesion ten days after treatment was begun. (*c*) Same lesion sixty-nine days after treatment was begun and fifty-one days after cessation. Note hyperpigmentation but absence of inflammatory activity.

On the seventh and eighth days the patient received 750 mg. every six hours. This dose was followed by doses of 1 Gm. every six hours until he had had a total of 56.5 Gm. of aureomycin in eighteen days.

By the fifth day of treatment resolution of the syphiloderms began and extended rapidly in all areas of involvement (figs. 2*b* and 3*b*).

The patient returned for observation sixty-nine days after treatment was begun, and on this examination the lesions of cutaneous syphilis were completely healed. Only hyperpigmentation, superficial atrophy and scarring remained (figs. 2*c* and 3*c*). There was no demonstrable change in the aortic regurgitation. The serologic reactions for syphilis were still positive, but the Kahn quantitative titer then measured 64 units.

CASE 4.—A white man 60 years of age came to the clinic because of asymptomatic cutaneous lesions of the right forearm, of six years' duration (fig. 4*a*), and a similar involvement of the right side of the forehead, of one year's duration.

Fig. 4 (case 4).—Late syphiloderm of right forearm of six years' duration. (*a*) Before treatment. (*b*) Same lesion seven days after oral administration of aureomycin was started. (*c*) Same lesion sixteen days after beginning of treatment.

Fig. 5 (case 4).—Specimen from forehead before treatment. Note dense infiltrates and presence of giant and epithelial cells.

A diagnosis of noduloulcerative cutaneous syphilis was made, which was confirmed by reports of positive serologic reactions for syphilis (Kline, Kahn, Hinton and Kolmer tests), with a quantitative titer of 256 Kahn units.

The rest of the physical and laboratory examinations were noncontributory. On examination the cerebrospinal fluid was observed to be normal.

Treatment with aureomycin was started with 250 mg. given every six hours by mouth. Within two days the lesions improved significantly. The dose was then increased to 1 Gm. every six hours, which the patient tolerated well for five days before nausea and vomiting began. The dose of aureomycin then was decreased to 500 mg. every six hours, which dose he tolerated without further difficulty. This dose was employed until the patient had received a total of 60 Gm. of aureomycin. Rapid resolution of the cutaneous infiltrate and rapid healing of the ulcerations occurred with this therapy (fig. 4*b* and *c*).

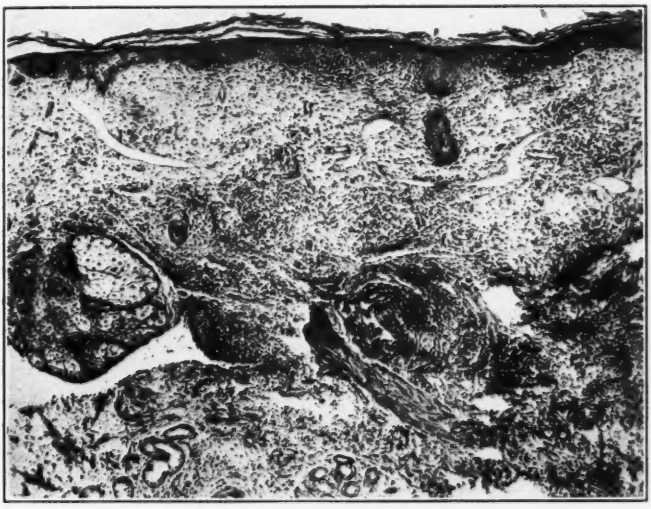

Fig. 6 (case 4).—Specimen from a site contiguous to that shown in figure 5, removed seven days after treatment was begun. This section exhibits much less infiltrate and microscopic changes correlative with the clinical improvement.

Comparisons of specimens removed from contiguous sites before treatment and on the seventh day after treatment was begun revealed appreciable disappearance of the pathologic infiltrate (figs. 5 and 6).

### NEUROSYPHILIS

Four patients with neurosyphilis were treated with aureomycin given by mouth. One patient with tabes dorsalis was given aureomycin, but because of gastrointestinal reactions administration of aureomycin was discontinued and penicillin was given intramuscularly. We are not reporting this case in detail, but reports on the other 3 cases of neurosyphilis follow.

CASE 5.—A white woman 42 years of age was a patient at the Rochester State Hospital, where the diagnosis of dementia paralytica was confirmed. Her difficulties had begun in February 1945 with forgetfulness, mental confusion and bizarre patterns of behavior which increased so that in May 1946 she was admitted to the University Hospitals, Minneapolis, and transferred in July to the Rochester State Hospital. A diagnosis of neurosyphilis of the dementia paralytica type was made, and she received malarial therapy, during which she had ten paroxysms, for a total of thirty-five hours of fever, with a rectal temperature of more than 104 F. This was followed by twelve injections of bismuth subsalicylate, one each week. Her mental condition steadily improved so that in April 1947 it was possible for her to be paroled. She returned again in September 1947, when she was given further

TABLE 3.—*Findings in Cerebrospinal Fluid in Case 5*

| Date | Kolmer | Protein, Mg. per 100 Cc. | Cell Count | Colloidal Gold Curve |
|---|---|---|---|---|
| 5/22/46 | 4+ | 153 | 72 small lymphocytes<br>12 polymorphonuclear cells | 5555542000 |
| 7/ 3/46 | 44444 | 100 | 88 small lymphocytes<br>11 polymorphonuclear cells | 5555532000 |
| | | Malarial Therapy | | |
| 10/15/36 | 4441 — | 30 | 1 small lymphocyte | 5553310000 |
| | | Administration of Bismuth Preparations | | |
| 2/11/47 | 44 — — — | 50 | 8 small lymphocytes | 5543210000 |
| 8/19/47 | 44 — — — | 60 | 11 small lymphocytes | 5543210000 |
| | | Cabinet Fever Therapy<br>Administration of Bismuth Preparations | | |
| 11/25/47 | 1 — — — — | 40 | 11 small lymphocytes<br>3 polymorphonuclear cells | 1222100000 |
| 7/ 6/48 | 422 — — | 100 | 26 small lymphocytes<br>3 polymorphonuclear cells | 5442100000 |
| 1/ 4/49 | 444 — — | 90 | 48 small lymphocytes<br>30 polymorphonuclear cells | 5554321000 |
| | | Aureomycin started 1/10/49 | | |
| 10 days* | 442 — — | 60 | 18 small lymphocytes | 5554320000 |
| 29 days* | 441 — — | 30 | 7 small lymphocytes | 5543210000 |
| 57 days* | 44 — — — | 45 | 4 small lymphocytes | 3422100000 |
| 72 days* | 4 — — — — | 50 | 5 small lymphocytes<br>occasional erythrocytes | 2322100000 |
| 100 days* | 43 — — — | 35 | 1 small lymphocyte | 0111000000 |
| 156 days* | 1 — — — — | 30 | 4 small lymphocytes | 0110000000 |
| 198 days* | doubtful | 25 | 3 small lymphocytes | 0222110000 |

* Period after treatment with aureomycin was started.

treatment with bismuth compounds and also cabinet hyperthermy because of a relapse in the findings observed in the cerebrospinal fluid. Another examination of the cerebrospinal fluid, in July 1948, revealed continued evidence of neurosyphilitic activity, but no further treatment was given.

In December 1948 this patient was admitted to the Rochester State Hospital for the third time with a history of increasing forgetfulness, difficulty in speech and poor coordination since October 1948. There had been several episodes of temporary stupor as well. The clinical evidences of dementia paralytica were apparent, but organic physical examination showed little except hyperactive tendon reflexes and a tremor of the tongue. The examination of the cerebrospinal fluid showed a dementia paralytica type of formula.

Aureomycin was administered by mouth from January 24 to February 25; during this time the patient received a total of 90.5 Gm. Nausea and occasional vomiting occurred when 1 Gm. was given every six hours, but the patient was able to tolerate 0.75 Gm. every six hours without difficulty.

The improvement in the cerebrospinal fluid findings is shown in table 3. The mental status to the time of the present report had shown some improvement; the patient had less euphoria, more lucid moments and less slurring of speech. No changes were noted in the reactions to serologic tests of the blood for syphilis; these remained positive throughout treatment.

CASE 6.—A white man aged 38 years came to the clinic because of a convulsive disorder, of two years' duration, which had gradually increased in frequency and in intensity. His history was unreliable because of euphoria, grandiose ideas and disoriented thinking. As far as could be ascertained there was no history of syphilis or its treatment.

TABLE 4.—*Findings in Cerebrospinal Fluid in Case 6*

| | Kolmer | Protein, Mg. per 100 Cc. | Cell Count | Colloidal Gold Curve |
|---|---|---|---|---|
| Before treatment | 44444 | 100 | 97 small lymphocytes<br>18 polymorphonuclear cells | 5555533100 |
| Time after beginning of treatment, days | | | | |
| 8 | 44441 | 100 | 25 small lymphocytes<br>1 polymorphonuclear cell | 5555310000 |
| 15 | 4443 — | 60 | 3 small lymphocytes | 5554310000 |
| 22 | 4442 — | 50 | 2 small lymphocytes | 5555421000 |
| 43 | 442 — — | 60 | 7 small lymphocytes<br>occasional erythrocytes | 5553220000 |

TABLE 5.—*Findings in Cerebrospinal Fluid in Case 7*

| | Kolmer | Protein, Mg. per 100 Cc. | Cell Count | Colloidal Gold Curve |
|---|---|---|---|---|
| Before treatment | Strongly positive 44444 | 100 | 110 small lymphocytes | 5554321000 |
| Time after beginning of treatment, days | | | | |
| 10 | Strongly positive 4444 | 100 | 42 small lymphocytes<br>1 polymorphonuclear cell | 5555432100 |
| 31 | Strongly positive 4443 | 70 | 29 small lymphocytes | 5554320000 |
| 46 | 4444 — | 50 | 13 small lymphocytes | 5553210000 |
| 117 | 44442 | 55 | 8 small lymphocytes | 5521100000 |

Physical examination gave essentially negative results except for the psychiatric evidence of acute dementia paralytica which was confirmed by the positive serologic reactions for syphilis in the blood and a dementia paralytica type of spinal fluid formula.

Oral treatment with aureomycin was started on March 8, 1949, and was continued until April 5, at which time a total of 63.5 Gm. had been given. It was difficult for the patient to tolerate 4 Gm. of aureomycin daily because of nausea and vomiting, and so it was necessary for us to vary the daily dose from 1 to 3 Gm. given in divided doses every six hours.

Within two weeks after medication was begun, the patient was less euphoric and belligerent and more cooperative and lucid; improvement continued. The reports on examinations of the cerebrospinal fluid are given in table 4.

CASE 7.—A white man aged 44 came to the clinic because of hernia of some thirty years' duration. A routine flocculation test for syphilis elicited a positive

reaction. Further investigation revealed positive Kline, Kahn, Hinton and Kolmer (Wassermann) reactions, with a quantitative Kahn titer of 256 units. Results of examinations of the cerebrospinal fluid are reported in table 5. There was no objective or subjective evidence of neurosyphilis, and a diagnosis of asymptomatic neurosyphilis was made. Treatment with aureomycin was begun on March 30, 1949, with a starting dose of 250 mg. daily. This dose was gradually increased until the patient was taking 1 Gm. daily. He has continued to receive 1 Gm. daily, which we believe is too small a dose. The findings in the cerebrospinal fluid before and during treatment are reported in table 5.

## COMMENT AND CONCLUSIONS

The beneficial effects of aureomycin in patients who have various forms of early and late syphilis are indicated by the results presented. Yet there are many unknown and unevaluated facets to the problem and to the eventual status of aureomycin as a syphilotherapeutic agent.

It is possible that there may be a synergistic action between aureomycin administered by mouth and penicillin given intramuscularly and that the concurrent administration of these antibiotics will give therapeutic results superior to those of either one alone. Aureomycin, too, should be of value for those patients in whom sensitivity to penicillin has developed, as well as for those whose conditions have demonstrated a resistance to penicillin and who have failed to show a favorable therapeutic response.

In many of our patients levels for aureomycin in the blood were determined at intervals during therapy. For the most part, when the administration of aureomycin by mouth was maintained at 250 mg. every four hours or 500 mg. every six hours, levels varied between 2 and 4 micrograms per cubic centimeter of blood serum, but when aureomycin was given in doses of 750 mg. every four hours, or 1 Gm. every six hours, levels of 4 to 8 micrograms per cubic centimeter of serum were frequently obtained. Recent work at the Mayo Clinic [5] indicated that therapeutically effective concentrations of aureomycin in blood serum may be expected when the antibiotic is given but two or three times daily. These same studies indicated that aureomycin is rather widely distributed throughout the tissues and readily traverses the blood-brain barrier and is present in the cerebrospinal fluid after the oral administration of amounts commonly used in the treatment of most infections. For example, the cerebrospinal fluid of 6 of 8 patients who were receiving aureomycin by mouth contained between 0.06 and 1.25 micrograms per cubic centimeter. The diffusion of aureomycin into the cerebrospinal fluid, unlike the diffusion of penicillin, appears not to depend on the presence or absence of actual inflammation. Aureomycin can be demon-

5. Herrell, W. E., and Heilman, F. R.: Aureomycin: Studies on Absorption, Diffusion and Excretion, Proc. Staff Meet., Mayo Clin. **24**:157-166 (March 30) 1949.

strated after oral administration in completely normal spinal fluid, as well as in spinal fluid obtained from patients suffering from meningeal irritation. Furthermore, it has been shown that aureomycin diffuses readily through the placenta and is readily available in the fetal circulation. This finding suggests that aureomycin should prove effective in the prevention and treatment of prenatal syphilis.

The total dose of aureomycin given in our 7 cases varied from 44.2 to 90.5 Gm. This variation is due principally to our lack of knowledge as to the optimal dose for the various types of syphilis; however, even now, more than five years after the introduction of penicillin for the treatment of syphilis, we do not know the ideal dosages for it. It seems, then, that if aureomycin should assume a high place in syphilotherapy many years of investigation will elapse before much can be said about proper dosage.

Untoward reactions of mild severity, limited to the gastrointestinal system, were frequent in our small series of patients. Anorexia and nausea were highest in frequency, followed by vomiting and occasional diarrhea.

Oral administration of a preparation in the treatment of such a disease as syphilis is certain to be criticized. Yet we feel definitely that for certain patients oral medication presents clearcut advantages. Even for the type of patients seen in the rapid treatment centers and charity clinics oral medication should present advantages of economy manifested through the greater ease of administration and, consequently, the need of less nursing care.

From this study we drew the following conclusions:

Aureomycin exhibits definite antisyphilitic activity.

Aureomycin should be of value for the treatment of the patient with syphilis which has become resistant to, or sensitive to, penicillin.

Oral medication has an advantage for certain patients.

The future will decide the ultimate place of aureomycin in syphilotherapy—the proper interval and total dose, whether it should be used alone or in concurrent administration with penicillin or other antibiotics and its therapeutic effectiveness in relation to time-proved heavy metal and antibiotic therapy.

Mayo Clinic.

# TREATMENT OF EARLY SYPHILIS WITH PENICILLIN AND BISMUTH SUBSALICYLATE

## Daily Injection of 500,000 Units of Penicillin G in Sodium Chloride Solution for Twenty Consecutive Days and Ten to Twenty Doses of Bismuth Subsalicylate at the Rate of Two a Week

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AND
OSVALDO A. PARDO, M.D.
HABANA, CUBA

THE PURPOSE of this paper is to show that constant hemoconcentrations of penicillin do not seem to be essential in the treatment of syphilis and that penicillin dissolved in sodium chloride solution and injected intramuscularly once a day appears to act as effectively in early syphilis as does penicillin in absorption-delaying menstruums.

Treatment of syphilis with penicillin must be made easy and not too expensive for the average patient. Injections every two or three hours cannot be used for the large mass of people suffering from syphilis, since hospitalization is required. Penicillin in absorption-retarding menstruums was therefore devised so that one or, at the most, two injections a day would be used; however, penicillin in oil and wax produced a high percentage of allergic reactions, some of them of such a severe type that patients refused further treatment. Penicillin in other vehicles as well as in chemical combinations such as procaine penicillin may be effective in one or two daily injections, but with these preparations the cost of the treatment is increased and the possbility of reactions in sensitized patients must be considered. The most recent acquisition, procaine penicillin G in oil with 2 per cent aluminum monostearate has been hailed as the most effective of all the preparations of penicillin, but its use is still too recent to allow definite conclusions. It may well be the preparation of choice if it is proved that one or two injections are sufficient to prolong the action of penicillin as long as ninety-six hours.

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From the Department of Dermatology and Syphilology, University of Habana, Medical School, service of Dr. V. Pardo-Castello.

Read at the Sixty-Ninth Annual Meeting of the American Dermatological Association, Inc., at Hot Springs, Va., May 27, 1949.

The ideal method for administering penicillin would be with the drug dissolved in sodium chloride solution injected once a day for a reasonably short period so that patients would accept this method of treatment willingly and abandonment of therapy could be reduced to a minimum. However, up to the present, penicillin in sodium chloride solution has been considered inadequate since it was assumed that sustained and constant blood levels of penicillin were necessary for effective results.

Lloyd-Jones, Allen and Donaldson [1] were the first, to the best of our knowledge, to point out that penicillin in water was effective in the treatment of early syphilis when given in daily injections of 300,000 units for eight to thirteen days, a total dose of between 2,400,000 and 3,900,000 units being used. The rate of failure was 9 per cent. The same authors treated 24 patients with single intravenous doses of 500,000 units daily for a period of five to seven days for total doses of 2,500,000 to 5,000,000 units, with a rate of failure of 4.2 per cent. In another series of cases 109 patients received daily intramuscular injections of 300,000 units of penicillin in water for eight to fifteen days for total doses of 2,400,000 to 4,500,000 units, with a rate of failure of 5.5 per cent. Four patients received daily single intramuscular injections of 500,000 units daily for eight days, with no relapses.

Moore [2] mentioned the observations of Lloyd-Jones and his collaborators, stating that they were not statistically comparable with the American data, but that "the immediate outcome seems favorable and the method worthy of further trial."

Moore [2] referred to the encouraging results obtained in a few cases at the Johns Hopkins Hospital when patients were treated with 600,000 units of penicillin in water at hourly intervals for three doses daily, for a total of 9,000,000 units in fifteen injections over five days.

Eagle [3] expressed the belief that large injections of penicillin are more effective than small injections, not because they provide higher absolute levels of penicillin but because they provide effective concentrations for longer periods.

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1. Lloyd-Jones, T. R.; Allen, S. J., and Donaldson, E. M.: Out-Patient Treatment of Early Syphilis with Penicillin: A Survey of Two Hundred and Fifteen Cases Treated by Single Daily Injections, Brit. M. J. **1**:567 (April 13) 1946.

2. Moore, J. E.: Penicillin in Syphilis, Springfield, Ill., Charles C Thomas, Publisher, 1946, p. 143.

3. Eagle, H.: Speculation as to the Therapeutic Significance of the Penicillin Blood Level, Ann. Int. Med. **28**:260 (Feb.) 1948.

More recently, Cohn, Rosenthal and Grunstein [4] insisted on the treatment of early syphilis with daily injections of penicillin in water. According to these authors the original concept that persistent levels of penicillin in the serum are necessary requires reconsideration with regard to syphilis at least, and, as previously reported, also as respects gonococcal infections. Most of the patients receiving penicillin by injection in sodium chloride solution or by mouth had no demonstrable levels of penicillin in the serum over a period of from seven to fourteen hours daily, and those receiving penicillin in water in oil emulsions had only irregular levels over a prolonged period, but the patients nevertheless responded to the different types of treatment. Therefore, it appears that the persistence of a serum penicillin level per se does not determine the final therapeutic outcome. Consequently it may be assumed that the action of penicillin on the invading organism in the tissues of the host last longer than is indicated by the presence of penicillin levels in the serum.

Jawetz [5] showed that this is also true for streptococci in mice. Tompsett, Timpanelli, Goldstein and McDermott [6] reported good results in the treatment of pneumonia with two daily injections of penicillin in water. After his experiments on mice infected with streptococci Zubrod [7] also expressed doubt as to the necessity of maintaining constant blood levels of penicillin.

White, Baker and Jackson (quoted by Cohn and associates [4]) found that the therapeutic results were the same with small, equally spaced doses of penicillin as an equivalent dose given in one or two injections daily. Cohn and his co-workers also found that low concentrations of penicillin acting over a long period were more effective than high concentrations acting over short periods.

Fleming [8] reported the fact that large doses of penicillin given intramuscularly in aqueous solution are just as effective in most infections as are small doses administered in repeated injections.

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4. Cohn, A.; Rosenthal, T., and Grunstein, I.: Observations on Patients with Early Syphilis Treated with Penicillin in Various Vehicles and by Oral Method, Am. J. Syph., Gonor. & Ven. Dis. **33**:27 (Jan.) 1949.

5. Jawetz, E.: Dynamics of the Action of Penicillin in Experimental Animals: Observations on Mice, Arch. Int. Med. **77**:1 (Jan.) 1946.

6. Tompsett, R.; Timpanelli, A.; Goldstein, O., and McDermott, W.: Discontinuous Therapy with Penicillin, J. A. M. A. **139**:555 (Feb. 26) 1949.

7. Zubrod, C. G.: Comparative Efficiency of Single and Multiple Dosage Regimens of Penicillin, Bull. Johns Hopkins Hosp. **81**:400 (Dec.) 1947.

8. Fleming A.: Como Debe Usarse la Penicilina, in Resúmenes de Publicaciones Médicas, New York, E. R. Squibb & Sons, 1948, vol. 3, p. 61.

The administration of penicillin in large doses in one day by Peters and Barton,[9] with amounts as high as 25,000,000 units given intravenously in continuous drip, was followed by such a high failure rate that this procedure had to be discarded. On the other hand, it has been demonstrated by many, including ourselves on the advice of Dr. J. E. Moore, that penicillin is more effective when its administration is prolonged for several days than when the same amount of the drug, regardless of vehicle, is administered in a short time.

Although there is considerable divergence of opinion on the subject, we believe that arsenic and bismuth preparations act synergically with penicillin and enhance the therapeutic value of any methed of treatment. Of these drugs the arsenic preparations are the most dangerous because of the severe reactions that they cause on the part of the skin, hematopoietic organs, liver and central nervous system. It would be desirable to find a method of treatment that would eliminate the arsenicals and combine penicillin with the less dangerous bismuth compounds.

Schoch and Alexander [10] showed that treatment of early syphilis with 1,200,000 units of penicillin plus five doses of bismuth subsalicylate in oil was more effective than the administration of penicillin alone, relapses being reduced in incidence and appearing at a later period.

Magnuson and Rosenau [11] stated that bismuth preparations and penicillin are synergistic in the treatment of experimental syphilis and that the optimum effect is obtained when the bismuth preparation is given in soluble form at such time that the two drugs may act simultaneously.

The purpose of our experiment in the treatment of early syphilis was to find an easy, relatively inexpensive and less time-consuming schedule so that the majority of our patients could be made to complete this treatment and, on the other hand, so that the percentage of failures would be reduced to a minimum. Ten weeks was found the longest time that our ambulatory hospital patients would willingly keep up a course of treatment. We decided therefore to try penicillin in sodium chloride solution in fairly large amounts daily, for a longer period than in the average schedule of treatment appearing in the litera-

9. Peters, E. E., and Barton, R. L.: The Massive Intravenous Penicillin Therapy of Early Syphilis, Am. J Syph., Gonor. & Ven. Dis. **32**:203 (May) 1948.

10. Schoch, A. G., and Alexander, L. J.: Treatment of Early Syphilis with Penicillin, J. A. M. A. **130**:696 (March 16) 1946.

11. Magnuson, H. J., and Rosenau, B. J.: Bismuth Plus Penicillin in the Treatment of Experimental Syphilis, Am. J. Syph., Gonor. & Ven. Dis. **32**:203 (May) 1948.

ture and with the use of a larger total amount of penicillin than heretofore advised for the treatment of early syphilis, on the assumption that sustained and constant blood levels of penicillin are not necessary for effective results, but to assure the daily presence of the therapeutically effective amounts of penicillin in the tissues for a longer time. We also decided to combine the antibiotic action of penicillin with the chemotherapeutic action of a bismuth preparation in a fairly large total amount divided into biweekly doses. The total amount of penicillin was 10,000,000 units divided into twenty intramuscular doses of 500,000 units each, administered daily in 3 cc. of sodium chloride solution. The total amount of bismuth subsalicylate was 1.30 to 2.60 Gm. divided into ten to twenty doses, administered twice a week for ten to twenty weeks,

*Distribution of Forty-Seven Patients by Race, Sex and Diagnosis at Beginning of Treatment*

| Race and Sex | Original Patients | | Distribution of Original Patients by Stage of Disease, Per Cent | | |
|---|---|---|---|---|---|
| | Number | Per Cent | Seronegative Primary | Seropositive Primary | Secondary |
| Negro, M. | 16 | 34 | 25 | 44 | 31 |
| Negro, F. | 9 | 20 | 00 | 22 | 78 |
| White, M. | 19 | 40 | 21 | 58 | 21 |
| White, F. | 3 | 6 | 00 | 00 | 100 |
| Total | 47 | 100 | 17 | 42.5 | 40.5 |

at the rate of 0.13 Gm. per dose. Thus the patient received daily treatment for twenty days and biweekly treatment for fifteen to fifty days longer.

Of the 47 patients whose cases are included in this report, 38, or 80 per cent, presented darkfield–positive lesions of early (primary or secondary) syphilis. The distribution of these patients according to race, sex and diagnosis at the beginning of treatment is shown in the accompanying table.

Thirty-four per cent of the patients were male Negroes; 20 per cent, female Negroes; 40 per cent, male white persons, and 6 per cent, female white persons. Of the entire group, for 42.5 per cent the diagnosis was seropositive primary syphilis, for 17 per cent seronegative primary syphilis and for 40.5 per cent secondary syphilis. Thus there was a similar percentage of cases for seropositive primary and for secondary syphilis

Of the female Negro group, 22 per cent (2 patients) had primary seropositive syphilis. They were the great-grandmother and grandmother of a congenitally syphilitic baby and were infected extragenitally on the left forearm in both cases. Both had darkfield–positive lesions.

Forty-three of the 47 patients in this study were below 40 years of age.

The study of possible Herxheimer reactions was limited to the febrile response. All the patients were carefully asked whether they had a rise in body temperature after the first dose of penicillin. For 20 patients, or 42.2 per cent, the answer was positive; the rest did not experience elevation of temperature.

Urticarial reactions were observed in 2 cases during the administration of penicillin. Diphenhydramine (benadryl®) hydrochloride in capsules three times a day for twenty-four hours and twice a day for the following forty-eight hours and in some cases once a day for three more days, controlled this type of reaction, and specific treatment was not interfered with.

Treponemes disappeared from open lesions in six hours after the first intramuscular injection of 500,000 units of crystalline penicillin G, dissolved in 3 cc. of sodium chloride solution.

Lesions healed rapidly. The healing time was difficult to measure, since the lesions were of different size and on different locations and there were many other variables which in our opinion make it impossible for us to point out more detailed information.

## RESULTS OF TREATMENT

Of the 47 patients starting this treatment in November 1947, 32 accepted and finished the ten week schedule of treatment and 9 completed the five week schedule of treatment, there thus being a total of 41 patients. The other 6 patients (11.7 per cent) became delinquent, and all efforts to bring them back to the clinic were fruitless.

The 41 patients completing the schedule treatment have been under observation for periods ranging from three to fifteen months, with an average follow-up of six months for the entire group. All the patients who were observed for one year or more were given spinal fluid examinations and had negative reactions.

At the time of presenting this report 26, or 63.4 per cent, have maintained or attained seronegativity. Excluding the 7 patients with primary seronegative cases, the serologic reversal was achieved in the entire group, independent of the initial titer, in an average period of

seventy-four days. The remaining 15 patients, or 36.6 per cent, are under observation with falling titer and no evidence of failure as manifested clinically, serologically or by seroresistance (persistent high titer) or syphilitic lesions resistant to treatment. No reinfections have occurred.

There was no difference in the clinical and the serologic response between the group that received 10 doses of bismuth and that which received 20 doses.

SUMMARY

This is a preliminary report on a schedule in progress in our syphilis clinic for the treatment of early syphilis with penicillin and bismuth preparations with 500,000 units of crystalline penicillin G dissolved in 3 cc. of sodium chloride solution injected intramuscularly once a day for twenty days, together with biweekly injections of 0.13 Gm. of bismuth subsalicylate for ten to twenty weeks. This schedule was completed by 41 patients, and the follow-up has been from three to fifteen months. There have not been any clinical or serologic relapses. There was no difference in results between the group that received 10,000,000 units of penicillin plus ten doses of bismuth subsalicylate and the group that received the same amount of penicillin plus twenty doses of the bismuth preparation.

This study was based on the belief that constant blood concentrations of penicillin were not necessary for the achievement of good results in the treatment of syphilis and that therefore no special menstruum was necessary to dissolve this antibiotic. We believe that penicillin is more effective when administered for a longer period, twenty days in our schedule, than that usually employed. We also believe that the use of a bismuth preparation in conjunction with penicillin enhances the value and effectivity of the treatment.

The good results obtained with this schedule cannot be taken as a norm for the treatment of all cases of early syphilis but should encourage further investigation along the same lines.

Glaxo Laboratories, Ltd., of England and the Commercial Solvents Corporation of New York helped in providing penicillin at cost and gave several free grants of the drug.

## ABSTRACT OF DISCUSSION ON PAPERS BY DRS. KIERLAND, O'LEARY AND HERRELL AND PARDO-CASTELLO AND PARDO

Dr. Udo J. Wile, Ann Arbor, Mich.: The last few years have seen revolutionary changes in the treatment of syphilis by the substitution of antibiotics for the previously employed heavy metals. This change has resulted in a faster rate of cure, with a greater percentage of success. What formerly was accomplished

in months or years is now measured by days and weeks. Notwithstanding this great advance, the treatment schedules and the philosophy of treatment are still in the same state of flux which for centuries has attended the treatment of syphilis. The papers of Drs. Pardo-Castello and Kierland are illustrative of this point. All investigators seem to agree that for the best therapeutic results it is necessary to employ crystalline penicillin G. The dosage, the time interval between injections, the menstruum in which the penicillin is dissolved and the question which Dr. Pardo-Castello has raised, that is, the necessity of a high blood concentration—these are all debatable issues.

It is somewhat difficult to compare Dr. Pardo-Castello's results with those following other schedules of treatment because he has used far more penicillin (a total of 10,000,000 units) than has been customarily used in other clinics and by other investigators.

The published results from several different sources seem to indicate that something like 90 per cent of cases of early syphilis can be made seronegative and maintain this status on doses between 2,400,000 and 4,000,000 units. In a general way these figures apply to penicillin in aqueous solutions, in oily suspensions and in combination with procaine and aluminum monostearate. It will be noted that of Dr. Pardo-Castello's 47 patients with early syphilis, 32 completed his ten week schedule and 26 of this number have maintained seronegativity. An additional 15 patients are under observation with falling titers, and it is safe to presume that these will achieve seronegativity later. While the total number of his cases is small compared with those of the Syphilis Study Group of the United States Public Health Service, his figures would seem to coincide or approximate those of other observers using both aqueous solution and oily suspensions.

Dr. Pardo-Castello has also brought up the interesting problem of bismuth preparations as possibly synergistic to penicillin in producing destruction of the spirochetes. Very extensive studies with a large number of patients receiving penicillin and a bismuth preparation and a large number receiving penicillin alone would have to be made in order for one to determine definitely whether the addition of the heavy metal enhances and/or increases the rapidity of cure with penicillin. From Dr. Pardo-Castello's figures it would appear that no better results were obtained from twenty injections of bismuth than were achieved with ten doses. The blood concentration of penicillin has always been a moot question. Generally speaking, one might presuppose that a therapeutic agent would be relatively more effective with a higher and prolonged concentration than with a low concentration and short residence in the blood stream. The firm belief in this hypothesis led to the incorporation of penicillin in oily vehicles which prevented its rapid absorption and so maintained a high blood concentration. It is quite possible that Dr. Pardo-Castello's view that high concentrations are not necessary is correct. Other investigators have held the same view. It may well be, however, that a larger amount of penicillin is necessary for the achievement of cure in the presence of low blood concentrations. As I have pointed out, Dr. Pardo-Castello's treatment schedule is considerably longer and stronger than schedules used elsewhere.

The continued observation of his already treated patients and the addition of several hundred more would throw considerable light on these questions.

I had the pleasure on a recent visit to Rochester of seeing 2 of the patients whose cases Dr. Kierland reported while they were receiving treatment with orally administered aureomycin. I was much impressed with the rapid involution which

took place in these 2 cases and in the other active cases which he reports. The use of aureomycin or any other antibiotic other than penicillin is based on the remote possibility that there may develop a penicillin-resistant strain of spirochetes or that isolated patients will react unfavorably or fail to respond entirely to penicillin G.

Dr. John Mahoney has investigated a large number of antibiotics for the reasons just mentioned. When I last heard him discuss the question, none of the antibiotics which he had investigated by that time had produced results comparable to those procured with penicillin.

It would appear from Dr. Kierland's paper that at least in early syphilitic cases the oral administration of aureomycin has shown the antibiotic to be an effective therapeutic agent in the few cases that have so far been investigated. It will be noted that Dr. Kierland makes no claim whatever that the oral route is a better method of administration, that aureomycin as yet has an ultimate place in syphilotherapy or that his figures are sufficiently large or his patients sufficiently followed to warrant any suggestions other than that the substance is worthy of continued investigation as another spirochetocidal antibiotic agent. Dr. Kierland would tell you that from the experimental side treatment with aureomycin is to date expensive. The present market price for aureomycin is about $1 for 250 mg. In anything but a subsidized clinic, the cost for the substance alone would be somewhere between $200 and $300 per case. No doubt with time aureomycin may be produced with much lower cost and others will be enabled to embark on this interesting research and to contribute the results and compare them with the figures now before us. I wish to express my admiration for the conservative manner in which Dr. Kierland presented his paper and to compliment Dr. Pardo-Castello on his good follow-up and on his ability to handle so many patients on a twenty consecutive day schedule.

Dr. Arthur J. Schoch, Dallas, Texas: Exceptionally good therapeutic results were indicated by Dr. Pardo-Castello's presentation concerning the use of 500,000 units of crystalline penicillin G daily for twenty days with the addition of biweekly injections of bismuth subsalicylate for an additional two to six weeks. Thus the over-all period of treatment varied from a minimum of one month to a maximum of two months.

On hypothetic grounds alone, this system of treatment should prove to be effective. Preliminary data presented by Dr. Pardo-Castello indicated that the observation period is sufficiently long to establish the system as good treatment for early syphilis. As would be expected, reactions to treatment are of no consequence.

Had this experiment been divided into two parts, namely, one with a group of patients receiving daily injections of soluble penicillin alone and another with a similar group receiving biweekly injections of bismuth subsalicylate alone, had the total number of patients in each group been approximately the same as the total group presented and had the observation period been the same, I feel relatively certain that the tentative conclusions would have been that both methods of treatment, on preliminary observation, were effective.

I thoroughly concur that constant blood levels in the treatment of early syphilis are not necessary. I am further of the opinion that determinations of penicillin blood levels are so vulnerable to factors of error that they are practically useless as a guide to the treatment of syphilis with penicillin.

I am still of the opinion that combining two therapeutic agents in the treatment of early syphilis is logical if one expects optimum results. However, I think that there now exists a problem in the treatment of early syphilis which is radically different from that which was present five years ago.

Five years ago the major question was, "Is it possible to cure in a short period the majority of patients—nay, the vast majority of patients—who have early syphilis by treatment with penicillin, with or without the addition of chemotherapeutic agents?" The answer to this question is indubitably, "Yes."

The paramount question today is, "How easily and how cheaply can this be done?" When one considers the mass treatment of early syphilis, it is mandatory to consider the expense. On the other hand, when one considers the occasional individual private patient for whom expense is no item, the factors of time and certainty of results are of utmost importance.

If one is forced to stipulate today what constitutes the best method of treatment for early syphilis, one would have to say that administration of crystalline penicillin G in aqueous or sodium chloride solution every two or three hours over a period of seven and a half days for a total dosage of at least 4,800,000 units occupies this enviable position.

At the other extreme we can list poor methods of treatment which, even over a period of seven and a half days, utilize a total dose of penicillin of less than 1,200,000 units. Even these methods, admittedly inadequate, cure over half of the patients with early syphilis.

In between are numerous schedules of treatment which must be considered good with respect to therapeutic results, and also with respect to time and expense involved.

Merely for sake of comparison, let me stipulate that poor methods of treatment in the modern sense cure about 60 per cent of all patients with early syphilis, good methods of treatment cure a little over 80 per cent and excellent methods of treatment cure a little over 90 per cent.

We should, therefore, visualize that new systems of treatment to be utilized in the treatment of early syphilis, whether they be applied to the management of indigent patients in large numbers or applied to private patients in small numbers, must be chosen on the basis of many collateral factors over and above that of therapeutic effectiveness.

Furthermore, mass treatment apparently requires standardization, which *ipso facto* groups together seronegative primary syphilis, seropositive primary syphilis and secondary syphilis. Even though one knows full well that the patient with seronegative primary syphilis is more certainly cured with a given system of treatment than is the next patient with florid secondary syphilis, it still seems imperative to group together these patients under the classification of persons with early infectious syphilis. On the other hand, where individualization is preferred and is usually expected, namely, in the case of the individual private patient, one must necessarily adapt the system of treatment to the problem at hand rather than adhere to broad principles of standardization.

In effect, there actually are two questions to be asked at present as to what is the best method of treatment of early syphilis: 1. "What is the best method of treatment for syphilis today to be applied to 40 or 50 patients per month at

the free Dallas Syphilis and Venereal Disease Clinic?" 2. "What method of treatment would I choose if a member of my family acquired early syphilis tomorrow?" The answer is perfectly definite in both instances.

Let me summarize by saying that treatment for early syphilis should be rapid and it should be safe for all. It should be inexpensive for the indigent, but good. Excellent treatment is available for those who can pay for and demand the best available.

Dr. Norman N. Epstein, San Francisco: It was indeed a pleasure to hear these two papers and the discussions which have followed. I was especially interested in the discussion on aureomycin as an antisyphilitic remedy. Those of us that deal with the problem of the treatment of syphilis realize that penicillin therapy is not the solution for all patients who come to us. We must recognize that there will be failures, sensitizations and possibly the development of resistance.

I should like to present an account of an experience that I had with a patient, a woman of 51 years of age, who came to see me on April 27, 1949. She had a confluent maculopapular eruption of secondary syphilis. Darkfield examination showed an occasional spirochete from a papule. Wassermann and Kahn tests of the blood gave strongly positive reactions. The patient was placed on treatment with procaine penicillin in oil, containing 2 per cent aluminum monostearate. Three hundred thousand units were given the first day. That night the patient had a Herxheimer reaction, with diarrhea and apparent fever. Treatment was continued from that time, with the administration of 600,000 units daily except Sunday. Her eruption faded, and her condition improved during the first week. On May 12, the same eruption which she had had over the body and face seemed to flare and increase in intensity. In spite of continued penicillin therapy up to the time that I left for this meeting, her lesions persisted. The brand of penicillin was changed from Schenley's to Bristol's flo-cillin "96"® without any obvious change. Darkfield examination was done on papules, but no spirochetes were found. Serologic tests on May 16 showed a very strongly positive Wassermann reaction. A biopsy of a papule showed an active inflammatory reaction compatible with secondary syphilis. From the fact that the cutaneous lesions had not been changed by therapy, we might conclude certainly that penicillin did not control the disease in this patient. I do not believe it was the fault of the penicillin per se or of the brand. Because of the fact that the penicillin was able only to alter the process and not to eradicate it, I believe we should call this case one of penicillin-resistant secondary syphilis. The introduction of a new remedy, such as Dr. Kierland presents, may be of value to patients who fail to improve or to be cured or who relapse.

Dr. Fred M. Jacob, Pittsburgh: I should like to ask Dr. Kierland whether he had any cases of Herxheimer reaction in his series of patients under treatment with aureomycin.

Dr. Howard Hailey, Atlanta, Ga.: With all present information considered, I believe a bismuth preparation to be the drug of choice in the treatment of syphilis. If I had syphilis and were limited to one drug, I should want 3 Gm. of bismuth subsalicylate in oil every five to seven days for a period of two years.

While I was a consultant at the Oliver General Hospital in Augusta, Ga., a young man was admitted with a chancre. He had a negative reaction to the Kahn test, as determined by two different laboratories. Neither laboratory had knowledge

of the double check. The patient received 7,000,000 units of penicillin. Later a classic secondary eruption appeared. The patient's blood reaction became positive. He was placed on therapy with bismuth preparations.

Dr. Martin T. Van Studdiford, New Orleans: We have tried all the antibiotics at Carville, and we are trying them in synergistic actions in the hope that where one does not affect some element the other one does and that in this way we will be able to carry on and better sterilize the patient of his bacilli. I wish to ask Dr. Kierland what reactions he has had with aureomycin and what the tolerance of his patients has been. A leper has a peculiar attitude toward therapy. He will stop any therapy that makes his fever go up or makes him feel worse. It is only through the application of psychology to a high degree that one can get these people to take drugs that make them feel worse. We are using aureomycin, streptomycin and penicillin in combination with the different sulfones. We have had some wonderful results with small doses of streptomycin with sulfones. Many patients haven't been able to tolerate aureomycin, but some are able to tolerate this treatment for ten day periods and then resume it after a rest period.

Dr. Charles R. Rein, New York: Drs. Kierland and Pardo-Castello are to be congratulated on their excellent presentations. There is no doubt that aureomycin administered by the oral route is an effective treponemicidal agent. Whether or not it will replace penicillin in therapy will depend on future developments. It may, however, be of great value in treating those patients with syphilis who may acquire a resistance to penicillin. The fact that Drs. Kierland and O'Leary found a high concentration of this antibiotic in spinal fluids does not necessarily attest to its greater efficacy in treating syphilis of the central nervous system. As ably pointed out by Dattner, penicillin has proved of great value in treating patients with such cases, even though the concentration in the spinal fluid has been negligible. The concentration of the antibiotic in the parenchymatous tissue is of the utmost importance. The level found in the spinal fluid is not as important because the treatment is directed toward the parenchymatous involvement and not toward the spinal fluid changes. Furthermore, there may be some objections to oral therapy with aureomycin and certain limitations to the routine use of that antibiotic because of its cost.

I should also like to comment on the presentation by Drs. Pardo-Castello and Pardo. Accumulated data by many investigators would indicate that there is no added advantage in the employment of adjuvant heavy metal therapy. Furthermore, better results have been obtained in shorter periods with procaine penicillin G in aluminum monostearate and oil than with the aqueous solutions of sodium salts of penicillin. At the present time we are interested in three studies employing the former type of penicillin preparations in early syphilis, as follows:

(1) Loveman—one injection of 1 cc. once a week for four weeks, for a total dose of 1,200,000 units; (2) Thomas, Rein and Kitchen—a single injection of 4 cc., for a total dose of 1,200,000 units, and (3) Arnold and Mahoney—a single injection of 1 cc., for a total dose of 300,000 units.

At least 250 patients have been treated by these schedules and have been followed clinically and serologically for as long as one year. The results to date have been excellent. We believe, therefore, that prolonged schedules employing

the aqueous solutions of sodium penicillin with adjuvant heavy metal therapy are not necessary. Furthermore, the number of patients who lapse from therapy increases as the duration of therapy is prolonged.

DR. V. PARDO-CASTELLO, Habana, Cuba: I want to correct a misunderstanding regarding patients receiving bismuth preparations as well as penicillin. Some received twenty and some ten doses of bismuth subsalicylate. There was no difference between the results in those taking ten doses of the bismuth preparation and in those taking twenty. It seems to me that most of us agree that the same amount of penicillin or bismuth preparation and arsphenamine is more effective when spread over a longer period than when given all at once. It has been proved beyond a doubt, it seems to me. Perhaps, with new procedures, treating syphilis and curing it in one day, one week or two weeks may be possible. However, I firmly believe that syphilis requires treatment for some time. Ten million units of penicillin administered in one day is far less effective than the same amount of penicillin given in twenty days. I am not alone in this belief. In the literature there are several references, which I did not have time to read, to the theory. The reason we started to use penicillin in a sodium chloride solution rather than in absorption-delaying solvents is that we observed, in conducting some experiments on the absorption-delaying action, that for the first six or eight hours after the injection there was a level of penicillin in the blood consistent with levels considered active or useful and that then there was a sudden drop lasting eight or nine hours, followed by a new rise in the concentration of penicillin in the blood. This could be explained only by the passage of penicillin from the tissues to the blood. A concentrated level of penicillin in the blood is unnecessary for effective therapeutic action. This statement was also considered true by Lloyd-Jones, of London, who found that penicillin in water is effective in the treatment of streptococcal infections. I feel that penicillin in water is just as effective as penicillin in any other menstruum. This seems to be so, too, in staphylococcal infections. It would be interesting to repeat these experiments and to know whether absorption delaying is really necessary for the treatment of syphilis.

DR. ROBERT R. KIERLAND, Rochester, Minn.: First, may I thank the discussers for their kind comments?

As indicated by Dr. Wile, the price of aureomycin at the present time is so high that its use in the treatment of the average patient with syphilis is prohibitive. Yet let us not forget that originally penicillin, too, was expensive. For the patient who is sensitive to penicillin or who becomes resistant to the effects of penicillin, as exemplified by Dr. Epstein's patient, aureomycin offers another available means of treatment.

We wish to make our point clear concerning oral medication. We feel that for certain patients oral medication presents a distinct advantage. Few will deny that it is easier to swallow a few capsules than to receive intramuscular injections. There are occasions in which oral medication is of decided advantage to patients of a higher social and economic status.

Dr. Jacob inquires whether Herxheimer reactions were observed. The first patient reported had a febrile Herxheimer reaction within twenty-four hours after receiving aureomycin. Only 1 person treated had a roseola, and the lesions did not flare after treatment with aureomycin. In the patients with late forms of syphilis no Herxheimer effects were noted.

In addition to the gastrointestinal reactions previously mentioned, one patient acquired photosensitivity, in the form of erythema solare, during therapy with aureomycin, which reaction persisted for a month after treatment was discontinued. Aside from the reactions mentioned, the patients tolerated aureomycin well, and in only one instance was it necessary to discontinue its administration. Some patients who cannot tolerate a dose of 4 Gm. daily may easily tolerate 2 Gm. daily.

We agree with Dr. Rein that high levels of the antibiotic in the cerebrospinal fluid do not indicate its therapeutic effect or superiority. We make no claim that aureomycin is superior to penicillin; however, on the basis of our experience with penicillin and other antisyphilitic remedies, we feel that the beneficial effects of aureomycin are equal to those of penicillin.

# VIRUSES OF SPECIAL INTEREST TO THE DERMATOLOGIST

## A Review

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THE PAST two decades have ushered in a new era in knowledge of the viruses and the diseases which they produce. An imposing array of new viral entities has been described and related to clinical disease. Tremendous gains have been made in understanding of the fundamental nature of these agents, their modes of dissemination and their relations to their hosts.

Along with these advances has come a realization of the difficulties to be encountered in the development of therapeutic substances for treating viral disease. The sulfonamides and antibiotics have been of little use in the treatment of viral diseases other than those caused by the viruses of the psittacosis–lymphogranuloma venereum group. Although many reports concerning the therapeutic effectiveness of various drugs in viral disease have appeared—and some of these will be mentioned in this paper—it must be remembered that most of these reports have neither been substantiated nor found general acceptance.

In the majority of viral diseases of particular interest to the dermatologist, the laboratory is of no assistance in establishing a diagnosis. In certain instances, the demonstration of elementary bodies and inclusions, typical of a given virus, may prove useful. In others the demonstration of a rise in specific antibody titer in the patient's serum during convalescence may help. But usually serologic data are of value only in retrospect because the patient may have recovered from his illness or died before the diagnosis is completed. Any attempt to isolate and identify the virus in a given infection is an involved procedure which is in the nature of investigative research and should be undertaken only with this view in mind.

### PSITTACOSIS–LYMPHOGRANULOMA VENEREUM GROUP

The psittacosis–lymphogranuloma venereum group is a term applied to a group of similar and closely related viruses. The classification of these viruses into one group is based on their striking simi-

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This paper in slightly modified form was presented before the Annual Meeting of the Bronx Dermatological Society, New York, on Dec. 16, 1948.

larities in morphologic and tinctorial characteristics and sharing of certain antigenic components.

The viruses of the group occur naturally as frank or latent infections in a wide variety of mammalian and avian species and give rise to several clinical entities in man.

The agents which comprise the psittacosis–lymphogranuloma venereum group include the viruses not only of psittacosis [1] and lymphogranuloma venereum [2] but also of ornithosis,[3] meningopneumonitis,[4] human pneumonitis (strains SF,[5] Louisiana [6] and Illinois [7]), spontaneous mouse pneumonitis [8] and feline pneumonitis [9] and, finally, the less definitely related viruses of trachoma and inclusion blennorrhea (inclusion conjunctivitis).

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1. Bedson, S. P., and Bland, J. O. W.: A Morphological Study of Psittacosis Virus, with the Description of a Developmental Cycle, Brit. J. Exper. Path. **13**:461-466 (Oct.) 1932.

2. Hellerström, S., and Wassen, E.: Meningoenzephalitische Veränderungen bei Affen mit Lymphogranuloma inguinale, Compt. rend. 8 Cong. Internat. de Dermat. et Syph., 1930, pp. 1147-1151. Levaditi, C.; Ravaut, P.; Lépine, P., and Schoen, R.: Etude étiologique et pathogénique de la maladie de Nicolas et Favre (lymphogranulomatose inguinale subaiguë, ulcère vénérien adénogène, poradénolymphite), Ann. Inst. Pasteur **48**:27-88 (Jan.) 1932. Findlay, G. M.: Experiments on Transmission of the Virus of Climatic Bubo (Lymphogranuloma Inguinale) to Animals, Tr. Roy. Soc. Trop. Med. & Hyg. **27**:35-66 (June) 1933.

3. (*a*) Meyer, K. F.; Eddie, B., and Yanamura, H. Y.: Ornithosis (Psittacosis) in Pigeons and Its Relation to Human Pneumonitis, Proc. Soc. Exper. Biol. & Med. **49**:609-615 (April) 1942. (*b*) Meyer, K. F., and Eddie, B.: Spontaneous Ornithosis (Psittacosis) in Chickens the Cause of a Human Infection, ibid. **49**:522-525 (April) 1942.

4. Francis, T., Jr., and Magill, T. P.: An Unidentified Virus Producing Acute Meningitis and Pneumonitis in Experimental Animals, J. Exper. Med. **68**:147-160 (Aug.) 1938.

5. Eaton, M. D.; Beck, M. D., and Pearson, H. E.: A Virus from Cases of Atypical Pneumonia: Relation to the Viruses of Meningopneumonitis and Psittacosis, J. Exper. Med. **73**:641-654 (May) 1941.

6. Olson, B. J., and Larson, C. L.: An Epidemic of a Severe Pneumonitis in the Bayou Region of Louisiana: V. Etiology, Pub. Health Rep. **60**:1488-1503 (Dec. 14) 1945.

7. Zichis, J., and Shaughnessy, H. J.: Isolation of an Apparently New Virus from Two Fatal Pneumonia Cases, Science **102**:301-302 (Sept. 21) 1945.

8. (*a*) Gönnert, R.: Die Bronchopneumonie, eine neue Viruskrankheit der Maus, Zentralbl. f. Bakt. (Abt. 1) **147**:161-174 (June 3) 1941. (*b*) Gordon, F. B., and Karr, H. V.: Morphology of a Virus Causing Pneumonitis in Mice, Proc. Inst. Med. Chicago **14**:370 (March 15) 1943. (*c*) Nigg, C., and Eaton, M. D.: Isolation from Normal Mice of a Pneumotropic Virus Which Forms Elementary Bodies, J. Exper. Med. **79**:497-510 (May) 1944. (*d*) DeBurgh, P.; Jackson A. V., and Williams, S. E.: Spontaneous Infection of Laboratory Mice with a Psittacosis-like Organism, Australian J. Exper. Biol. & M. Sc. **23**:107-110 (June) 1945.

9. Baker, J. A.: A Virus Causing Pneumonia in Cats and Producing Elementary Bodies, J. Exper. Med. **79**:159-172 (Feb.) 1944.

All the viruses of the group are represented by typical elementary bodies of around 220[10] to 450[11] millimicrons in diameter and form basophilic, cytoplasmic inclusion bodies several microns in diameter. All the viruses of the group apparently undergo a similar life cycle,[12] which can be readily observed in suitably prepared materials under the ordinary microscope. Shortly after invasion of the cell, the virus particle or elementary body undergoes slight enlargement to become what is called an initial body. The initial bodies may undergo multiplication by fission. These structures then gradually increase in size to form large inclusion bodies called plaques. Eventually, the plaques rupture, releasing numerous elementary bodies which in turn infect new cells and repeat the life cycle. An alternate life cycle is observed when the virus enters a presumably damaged cell. In this instance, the elementary bodies grow dispersely throughout the cytoplasm without the formation of plaques. It is generally accepted that the plaque should be considered a colony of virus particles surrounded by a matrix of viral or cellular origin.

The viruses of the psittacosis–lymphogranuloma venereum group may be propagated in a wide variety of hosts, including mammals, birds, tissue culture and the fertile egg. Although considerable selectivity for certain tissues or routes of inoculation is manifest, all these viruses, except those of trachoma and inclusion conjunctivitis, grow abundantly in the mouse lung and the yolk sac of the fertile egg. These tissues constitute the chief sources of virus in experimental investigations.

There is no simple means for differentiating the members of the psittacosis–lymphogranuloma venereum group from one another. While establishment of a given virus as a member of the group is readily accomplished by the complement fixation test, identification of the individual virus falls into the realm of investigative research. There are five main bases for differentiation which have been developed.

The first involves the use of pathogenicity tests[13] in mammals, in birds and in the embryonated egg. Through inoculation of these

10. Levinthal, W.: Recent Observations on Psittacosis, Lancet **1**:1207-1210 (May 25) 1935.

11. Kurotchkin, T. J.; Libby, R. L.; Gagnon, E., and Cox, H. R.: Size and Morphology of the Elementary Bodies of the Psittacosis-Lymphogranuloma Group of Viruses, J. Immunol. **55**:283-287 (March) 1947.

12. Bedson and Bland.[1] Findlay, G. M.; Mackenzie, R. D., and MacCallum, F. O.: A Morphological Study of the Virus of Lymphogranuloma Inguinale (Climatic Bubo), Tr. Roy. Soc. Trop. Med. & Hyg. **32**:183-188 (Aug.) 1938. Rake, G., and Jones, H. P.: Studies on Lymphogranuloma Venereum: I. Development of the Agent in the Yolk Sac of the Chicken Embryo, J. Exper. Med. **75**: 323-338 (March) 1942.

13. (*a*) Meyer, Eddie and Yanamura.[3a] (*b*) Eaton, Beck and Pearson.[5] (*c*) Nigg and Eaton.[8c] (*d*) Pinkerton, H., and Moragues, V.: Comparative Study of

animals by a variety of routes, it is possible for one to demonstrate differences with respect to infectivity, lethality and the establishment or failure of establishment of a carrier state.

A second method, involving a determination of sensitivity to sulfonamide drugs,[14] has proved useful in the separation of certain strains of the viruses of psittacosis–lymphogranuloma venereum, mouse pneumonitis, trachoma and inclusion conjunctivitis from the other agents of the group.

The third means for differentiation is the cross immunity test.[15] Laboratory animals, usually mice, are immunized with sublethal amounts of live virus or killed virus and subsequently challenged with homologous and heterologous strains of virus. While some cross immunity is evident, pronounced differences in these viruses, corresponding roughly to results of pathogenicity tests, are obtained.

A fourth method consists of toxin neutralization tests. Rake and his associates [16] showed that the viruses of the group grown in the fertile egg produced toxins which were lethal to mice on intravenous injection. These toxins were specifically neutralized by antiserums prepared in rabbits and chickens. Serums from human patients were likewise specific.

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Meningopneumonitis Virus, Psittacosis of Pigeon Origin and Psittacosis of Parrot Origin, J. Exper. Med. **75**:575-580 (June) 1942. (*e*) Beck, M. D.; Eaton, M. D., and O'Donnell, R.: Further Laboratory Studies on the Classification of Psittacosis-like Agents, ibid. **79**:65-77 (Jan.) 1944. (*f*) Hamre, D. M., and Rake, G.: Feline Pneumonitis (Baker): A New Member of the Lymphogranuloma-Psittacosis Group of Agents, J. Infect. Dis. **74**:206-211 (May-June) 1944.

14. (*a*) Hamre and Rake.[13f] (*b*) Rake, G.; Jones, H. P., and Nigg, C.: Sulfonamide Chemotherapy of Mouse Pneumonitis, Meningopneumonitis and Lymphogranuloma Venereum, Proc. Soc. Exper. Biol. & Med. **49**:449-452 (March) 1942. (*c*) Rake, G.; Shaffer, M. F., and Thygeson, P.: Relationship of Agents of Trachoma and Inclusion Conjunctivitis to Those of Lymphogranuloma-Psittacosis Group, ibid. **49**:545-547 (April) 1942. (*d*) Hamre, D., and Rake, G.: Studies on Lymphogranuloma Venereum: V. The Action of Some Antibiotic Substances and Sulfonamides in Vitro and in Vivo upon the Agents of Feline Pneumonitis and Lymphogranuloma Venereum, J. Infect. Dis. **81**:175-190 (Sept.-Oct.) 1947.

15. (*a*) Eaton, Beck and Pearson.[5] (*b*) Nigg and Eaton.[8e] (*c*) Beck, Eaton and O'Donnell.[13e] (*d*) Eaton, M. D.; Martin, W. P., and Beck, M. D.: The Antigenic Relationships of the Viruses of Meningopneumonitis and Lymphogranuloma Venereum, J. Exper. Med. **75**:21-33 (Jan.) 1942.

16. Hamre and Rake.[13f] Rake, G., and Jones, H.: A Toxic Factor Associated with the Agent of Lymphogranuloma Venereum, Proc. Soc. Exper. Biol. & Med. **53**:86-88 (May) 1943; Studies on Lymphogranuloma Venereum: II. The Association of Specific Toxins with Agents of Lymphogranuloma-Psittacosis Group, J. Exper. Med. **79**:463-486 (May) 1944.

The fifth method is the neutralization of viral infectivity by antiserum prepared in chickens.[17] Chicken antiserums prepared against these viruses exhibit a high degree of specificity in the neutralization test and provide a ready means for differentiation. The relations shown in the serum neutralization test agree with the findings obtained by the use of the other methods described.

The complement fixation test is most valuable in identifying the viruses of the psittacosis–lymphogranuloma venereum group but is of no value in differentiating the individual members of the group. Except in a few isolated instances [18] in which animal serums were used, the complement fixation test has shown a broad antigenic similarity and failed to differentiate between these viruses.[19] The complement fixation test has, however, found considerable usefulness in the diagnosis of infection with this group of viruses in man. Although the specific virus involved in a particular infection cannot be distinguished by the complement fixation test at present, infection with a virus of the psitta-

17. Hilleman, M. R., and Gordon, F. B.: Immunologic Relations of the Psittacosis-Lymphogranuloma Group of Viral Agents, Proc. Soc. Exper. Biol. & Med. **56**:159-161 (June) 1944. Hilleman, M. R.: Immunological Studies on the Psittacosis-Lymphogranuloma Group of Viral Agents, J. Infect. Dis. **76**:96-114 (March-April) 1945. Kempf, A. H.; Wheeler, A. H., and Nungester, W. J.: Isolation of an Agent Belonging to the Psittacosis-Lymphogranuloma Group of Viruses, ibid. **76**:135-143 (March-April) 1945. St. John, E., and Gordon, F. B.: Studies on the Immunological Relationships of the Psittacosis-Lymphogranuloma Venereum Group of Viruses, ibid. **80**:297-306 (May-June) 1947.

18. (*a*) Eaton, Martin and Beck.[15d] (*b*) Eddie, B., and Francis, T., Jr.: Occurrence of Psittacosis-like Infection in Domestic and Game Birds of Michigan, Proc. Soc. Exper. Biol. & Med. **50**:291-295 (June) 1942. (*c*) Thomas, L., and Kolb, E. M.: Relationship of the Virus of Cat Pneumonia (Baker) to the Psittacosis-Lymphogranuloma Group of Agents, ibid. **54**:172-174 (Nov.) 1943 (*d*) Smadel, J. E.; Wertman, K., and Reagan, R. L.: Yolk Sac Complement Fixation Antigen for Use in Psittacosis-Lymphogranuloma Venereum Group of Diseases, ibid. **54**:70-74 (Oct.) 1943.

19. (*a*) Eaton, Martin and Beck.[15d] (*b*) Smadel, Wertman and Reagan.[18d] (*c*) Rake, G.; Eaton, M. D., and Shaffer, M. F.: Similarities and Possible Relationships Among Viruses of Psittacosis, Meningopneumonitis and Lymphogranuloma Venereum, Proc. Soc. Exper. Biol. & Med. **48**:528-531 (Nov.) 1941. (*d*) Eaton, M. D., and Corey, M.: Complement-Fixation in Human Pneumonitis with Group-Reactive Virus Antigens, ibid. **51**:165-168 (Oct.) 1942. (*e*) Bowser, B. M., and Nigg, C.: Studies on Lymphogranuloma Venereum Complement-Fixing Antigens: II. Serological Studies with Boiled Phenolized Antigens, J. Immunol. **53**:269-275 (July) 1946. (*f*) Hilleman, M. R., and Nigg, C.: Studies on Lymphogranuloma Venereum Complement-Fixing Antigens: IV. Fractionation with Organic Solvents of Antigens of the Psittacosis-Lymphogranuloma Venereum Group, ibid. **59**:349-364 (Aug.) 1948. (*g*) Hilleman, M. R., and Helmold, R. J.: Indirect Complement Fixation Test for Psittacosis-Lymphogranuloma Venereum Group Antibodies in Chicken Antisera, Federation Proc. (pt. 1) **8**:405 (March) 1949.

cosis–lymphogranuloma venereum group can be determined with a considerable degree of certainty.

Several different types of complement-fixing antigens, utilizing infected mouse spleen [20] or lung,[21] yolk sac,[22] allantoic fluid [15d] and tissue culture,[23] have been developed. Various procedures were utilized in the preparation of these antigens to inactivate the virus, enhance the activity and effect the maximal purity and specificity.

Knowledge of the antigenic composition of these viruses is limited, but beginning investigations in this direction have been made. The existence of heat-stable,[24] heat-labile [24c] and water-soluble [25] antigens has been demonstrated. Further, an ether-soluble,[26] presumably lipid, antigen has been described. This ether-soluble antigen was purified by successive precipitation with alcohol and acetone and shown to be active only in the presence of lecithin of egg or vegetable origin. The purified ether extract antigen and a residual antigen not soluble in ether were shown to be group-reactive in the complement fixation test, like all other antigens for this group which have been developed to the present time.

Chemotherapy of diseases caused by viruses in the psittacosis–lymphogranuloma venereum group has been extensively investigated both experimentally and clinically, and most encouraging results have been obtained. Although influenced to some extent by the method of testing and the quantity of antiviral substance used, the results of

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20. Bedson, S. P.: Observations on the Complement-Fixation Test in Psittacosis, Lancet **2**:1477-1480 (Dec. 25) 1937.

21. McKee, C. M.; Rake, G., and Shaffer, M. F.: Complement Fixation Test in Lymphogranuloma Venereum, Proc. Soc. Exper. Biol. & Med. **44**:410-413 (June) 1940.

22. (*a*) Smadel, Wertman and Reagan.[18d] (*b*) Bowser and Nigg.[19e] (*c*) Hilleman and Nigg.[19f] (*d*) McKee, Rake and Shaffer.[21] (*e*) Nigg, C.; Hilleman, M. R., and Bowser, B. M.: Studies on Lymphogranuloma Venereum Complement-Fixing Antigens: I. Enhancement by Phenol or Boiling, J. Immunol. **53**:259-268 (July) 1946. (*f*) Shaffer, M. F., and Rake, G.: Studies on Lymphogranuloma Venereum: Evaluation of the Complement Fixation Test with Lygranum, J. Lab. & Clin. Med. **32**:1060-1086 (Sept.) 1947.

23. Meyer, K. F., and Eddie, B.: The Value of the Complement Fixation Test in the Diagnosis of Psittacosis, J. Infect. Dis. **65**:225-233 (Nov.-Dec.) 1939.

24. (*a*) Bowser and Nigg.[19e] (*b*) Nigg, Hilleman and Bowser.[22e] (*c*) Bedson, S. P.: Observations Bearing on the Antigenic Composition of Psittacosis Virus, Brit. J. Exper. Path. **17**:109-121 (April) 1936.

25. Rake, G.; Shaffer, M. F.; Jones, H. P., and McKee, C. M.: Soluble Antigen in Lymphogranuloma Venereum, Proc. Soc. Exper. Biol. & Med. **46**:300-303 (Feb.) 1941.

26. Hilleman and Nigg: Studies on Lymphogranuloma Venereum Complement-Fixing Antigens: III. The Solubility in Ether of an Active Fraction, J. Immunol. **53**:201-208 (June) 1946. Footnote 19f.

research on chemotherapy in this group have been in general agreement (see Hamre and Rake [14d] for a review).

With the probable exception of the virus of inclusion conjunctivitis,[27] all the viruses of the psittacosis–lymphogranuloma venereum group appear to be susceptible to penicillin either under experimental conditions or in clinical trials in human patients infected with these viruses, or in both.[28] Only the viruses of lymphogranuloma venereum, mouse pneumonitis, psittacosis, trachoma and inclusion blenorrhea are susceptible to the sulfonamides.[29] Ornithosis, meningopneumonitis, feline pneumonitis and human pneumonitis strains SF and Louisiana are not susceptible to these drugs.[30]

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27. Thygeson, P., in Rivers, T. M.: Viral and Rickettsial Infections of Man, Philadelphia, J. P. Lippincott, 1948, chap. 17, p. 367. Sorsby, A.: Local Penicillin Therapy in Ophthalmia Neonatorum, Brit. M. J. **1**:903-906 (June 30) 1945. Sorsby, A., and Hoffa, E.: Local Penicillin Therapy in Ophthalmia Neonatorum, ibid. **1**:114-115 (Jan. 27) 1945.

28. (*a*) Hamre and Rake.[14d] (*b*) Heilman, F. R., and Herrell, W. E.: Penicillin in the Treatment of Experimental Ornithosis, Proc. Staff Meet., Mayo Clin. **19**:57-65 (Feb. 9) 1944. (*c*) Turgasen, F. E.: Human Ornithosis Treated with Penicillin, J. A. M. A. **126**:1150-1151 (Dec. 30) 1944. (*d*) Darius, D. J.: Penicillin Treatment of Trachoma: A Preliminary Report, Am. J. Ophth. **28**:1007 1009 (Sept.) 1945. (*e*) Flippin, H. F.; Gaydosh, M. J., and Fittipoldi, W. V.: Treatment of Human Psittacosis with Penicillin, J. A. M. A. **128**:280-281 (May 26) 1945. (*f*) Gilford, G. H.: Treatment of Trachoma with Penicillin, Correspondence, Brit. M. J. **1**:232-233 (Feb. 17) 1945. (*g*) Thygeson, P.: The Diagnosis and Treatment of Trachoma: A Report of Nineteen Cases in Military Personnel, Mil. Surgeon **97**:355-361 (Nov.) 1945. (*h*) Wiseman, R. W.; Meikeljohn, G.; Lackman, D. B.; Wagner, J. C., and Beveridge, G. W.: Studies on the Chemotherapy of Viruses in the Psittacosis-Lymphogranuloma Group: II. Effect of Penicillin and Sulfadiazine on Seven Strains in Mice, J. Immunol. **54**:9-16 (Sept.) 1946. (*i*) Early, R. L., and Morgan, H. R.: Studies on Chemotherapy of Viruses in the Psittacosis-Lymphogranuloma Venereum Group: IV. Effect of Certain Chemotherapeutic Agents on Psittacosis Virus (6 B.C. Strain) Infections in Mice, ibid. **53**:251-257 (July) 1946. (*j*) Eaton, M. D.; Dozois, T. F.; van Allen, A.; Parish, V. L., and Schwalm, S.: Studies on Inhibition of the Agents of Murine and Feline Pneumonitis by Penicillin, ibid. **58**:251-267 (March) 1948.

29. (*a*) Rake, Jones and Nigg.[14b] (*b*) Wiseman, Meikeljohn, Lackman, Wagner and Beveridge.[28h] (*c*) Thygeson, P.: Treatment of Inclusion Conjunctivitis with Sulfanilamide, Arch. Ophth. **25**:217-227 (Feb.) 1941. Eaton, M. D., and Hanford, V. L.: Effect of the Host in Action of Sulfonamides on Elementary-Body Agents of Murine and Feline Pneumonitis, Proc. Soc. Exper. Biol. & Med. **59**:63-66 (May) 1945. Jones, H.; Rake, G., and Stearns, B.: Studies on Lymphogranuloma Venereum: III. The Action of the Sulfonamides on the Agent of Lymphogranuloma Venereum, J. Infect. Dis. **76**:55-69 (Jan.-Feb.) 1945. Meikeljohn, G.; Wagner, J. C., and Beveridge, G. W.: Studies on the Chemotherapy of Viruses in the Psittacosis-Lymphogranuloma Group: I. Effect of Penicillin and Sulfadiazine on Ten Strains in Chick Embryos, J. Immunol. **54**:1-8 (Sept.) 1946.

30. Rake, Jones and Nigg.[14b] Hamre and Rake.[14d] Wiseman, Meikeljohn, Lackman, Wagner and Beveridge.[28h]

Chloramphenicol (chloromycetin®) has been shown to possess considerable therapeutic activity against psittacosis and lymphogranuloma venereum viruses in eggs and mice infected with these viruses.[31] Aureomycin has proved highly promising in the treatment of human cases of lymphogranuloma venereum [32] and inclusion conjunctivitis.[33]

### LYMPHOGRANULOMA VENEREUM (CLIMATIC BUBO)

Lymphogranuloma venereum is caused by a virus belonging to the psittacosis–lymphogranuloma venereum group. The virus is pathogenic for mice, monkeys, apes, guinea pigs, cotton rats, hamsters and embryonated eggs. Infected mouse lung and brain and the yolk sac of the fertile egg are the most commonly used sources of virus for investigative and other purposes.

Although lymphogranuloma venereum is primarily a disease of the genital and anorectal regions, central nervous system [34] and ocular [35] infections have occurred.

The dermal sensitivity to lymphogranuloma venereum, which usually appears in patients with this disease, was utilized by Frei [36] in the development of the skin test for lymphogranuloma venereum. The Frei antigen, as originally described, consisted of sterile heated pus from an unruptured bubo of a patient with the disease. Antigens prepared from infected mouse brain [37] and purified elementary body suspensions [38] of yolk sac origin have also proved satisfactory. More

31. Smadel, J. E., and Jackson, E. B.: Effect of Chloromycetin on Experimental Infection with Psittacosis and Lymphogranuloma Venereum Viruses, Proc. Soc. Exper. Biol. & Med. **67**:478-483 (April) 1948.

32. Wright, L. T.; Sanders, M.; Logan, M. A.; Prigot, A., and Hill, L. M.: Aureomycin: A New Antibiotic with Virucidal Properties; I. A Preliminary Report on Successful Treatment in Twenty-Five Cases of Lymphogranuloma Venereum, J. A. M. A. **138**:408-412 (Oct. 9) 1948.

33. Braley, A. E., and Sanders, M.: Aureomycin in Ocular Infections: A Preliminary Report, J. A. M. A. **138**:426-427 (Oct. 9) 1948.

34. Sabin, A. B., and Aring, C. D.: Meningoencephalitis in Man Caused by the Virus of Lymphogranuloma Venereum, J. A. M. A. **120**:1376-1381 (Dec. 26) 1942. Beeson, P. B.; Wall, M. J., and Heyman, A.: Isolation of Lymphogranuloma Venereum from Blood and Spinal Fluid of a Human Being, Proc. Soc. Exper. Biol. & Med. **62**:306-307 (June) 1946.

35. Curth, W.; Curth, H. O., and Sanders, M.: Chronic Conjunctivitis Due to the Virus of Venereal Lymphogranuloma, J. A. M. A. **115**:445-447 (Aug. 10) 1940.

36. Frei, W.: Eine neue Hautreaktion bei "Lymphogranuloma inguinale," Klin. Wchnschr. **4**:2148-2149 (Nov. 5) 1925.

37. Grace, A. W., and Suskind, F. H.: Lymphogranuloma Inguinale: III. The Use of Lymphogranulomatous Mouse Brains for Diagnosis, Arch. Dermat. & Syph. **34**:65-78 (July) 1936.

38. Grace, A. W.; Rake, G., and Shaffer, M. F.: A New Material (Lygranum) for Performance of the Frei Test for Lymphogranuloma Venereum, Proc. Soc. Exper. Biol. & Med. **45**:259-263 (Oct.) 1940.

recently an antigen [39] prepared from saline suspensions of yolk sacs infected with the virus of lymphogranuloma venereum and inactivated with urea or phenol has been developed. This material is very reactive and can therefore be used in high dilution with satisfactory results. In evaluating the significance of a positive skin test, one must bear in mind that dermal sensitivity in lymphogranuloma venereum is psittacosis–lymphogranuloma venereum group reactive and that infection with other viruses of the psittacosis–lymphogranuloma venereum group will also evoke a positive reaction.[40]

Laboratory diagnosis of lymphogranuloma venereum involves the demonstration of rise in antibody titer in the patient's serum. The demonstration of typical elementary bodies and inclusions in smears of pus or biopsy material from persons with the disease may also prove useful. Isolation and identification of the virus is an involved procedure and at present falls into the realm of investigative research.

The complement fixation test has found widespread usefulness in the diagnosis of lymphogranuloma venereum. The complement fixation test becomes positive earlier in the infection than does the Frei reaction [41] and is conceded to be the more sensitive test.[42] It must be remembered that the complement fixation test, like the skin test, is psittacosis–lymphogranuloma venereum group reactive and that the results of positive tests must be evaluated in the light of clinical findings and the patient's history.

Sulfonamide therapy has proved highly effective in the treatment of lymphogranuloma venereum.[43] Wright and his associates reported successful therapy with aureomycin.[32] The early experimental results obtained in the treatment of infected mice and eggs with chloramphenicol are promising,[31] but this drug has not been tried clinically in treatment of patients with lymphogranuloma venereum. Although penicillin has generally proved ineffective [44] in treatment of lymphogranuloma

39. Nigg, C.; Grace, A. W., and Hilleman, M. R.: On Use of Urea- and Phenol-Treated Skin Test Antigens for Diagnosis of Lymphogranuloma Venereum, Proc. Soc. Exper. Biol. & Med. **64**:416-418 (April) 1947.

40. Levine, S.; Holder, E. C., and Bullowa, J. G. M.: Complement Fixation for Lymphogranuloma Venereum and for Psittacosis with Frei Reactions Among Pneumonia Patients, J. Immunol. **46**:183-188 (April) 1943. Kilham, L.: A Skin-Test Antigen Common to Five Viruses of the Psittacosis-Lymphogranuloma Group, ibid. **60**:157-165 (Sept.) 1948.

41. Harrop, G. A.; Rake, G. W., and Shaffer, M. F.: New Clinical Conceptions of Lymphogranuloma Venereum, Tr. A. Am. Physicians **56**:101-105, 1941.

42. Rake, G.; Shaffer, M. F.; Grace, A. W.; McKee, C. M., and Jones, H. P.: New Aids in the Diagnosis of Lymphogranuloma Venereum, Am. J. Syph., Gonor. & Ven. Dis. **25**:687-698 (Nov.) 1941.

43. Grace, A. W.: Lymphogranuloma Venereum, Bull. New York Acad. Med. **17**:627-646 (Aug.) 1941.

44. McElligott, G. L. M., in Fleming, A.: Penicillin: Its Practical Application, London, Butterworth & Co., Ltd., 1946.

venereum, beneficial results have been reported attending the administration of penicillin in oil [45] and the use of local [46] penicillin therapy.

### TRACHOMA

Trachoma is caused by a virus which may be a member of the psittacosis–lymphogranuloma venereum group. Research on this disease has been badly handicapped through lack of suitable experimental animals. Apes, baboons and monkeys are susceptible to trachoma,[47] but pannus formation and cicatrization, typical of human infection, are not produced in these animals.

Diagnosis of trachoma is based on clinical findings and the demonstration of typical elementary bodies and inclusions in conjunctival scrapings stained by the Giemsa or Macchiavello technic. Complement fixation in low titer by patient's serum with the use of lymphogranuloma venereum antigen has been demonstrated [14c] but is of little diagnostic value.

Sulfonamide therapy is highly effective for trachoma,[48] especially when administration of the drug is begun early in the disease. Beneficial effects have been claimed for penicillin.[49]

### INCLUSION BLENNORRHEA (INCLUSION CONJUNCTIVITIS, SWIMMING POOL CONJUNCTIVITIS)

Inclusion blennorrhea is primarily an inflammatory disease of the eyes of newborn infants but may sometimes occur in adults. The disease in infants is acquired from the mother during passage through the birth canal, where the virus causes an infection of the cervix.[50] The virus has also been found in the male genital tract in association with a mild urethritis.[50] The genitourinary disease is probably widespread throughout the human population.

Occasionally, inclusion conjunctivitis is contracted in swimming pools, in which event the term "swimming pool conjunctivitis" has been applied.

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45. Willcox, R. R.: Simplified Penicillin Treatment of Lymphogranuloma Inguinale and Other Venereal Diseases in West African Troops, Post-Grad. M. J. **22**:97-98 (March) 1946.

46. Mayne, G. O., and Bain, A. D.: Local Penicillin in Lymphogranuloma Inguinale, Brit. J. Ven. Dis. **23**:40 (March) 1947.

47. Julianelle, L. A., and Harrison, R. W.: Transmissibility of Trachoma to Monkeys, Am. J. Ophth. **16**:857-862 (Oct.) 1933. Thygeson, P., and Proctor, F. I.: The Filterability of Trachoma Virus, Arch. Ophth. **13**:1018-1021 (June) 1935.

48. Thygeson.[28g] Loe, F.: Sulfanilamide Treatment of Trachoma: Preliminary Report, J. A. M. A. **111**:1371-1372 (Oct. 8) 1938.

49. Darius.[28d] Gilford.[28f]

50. Thygeson, P., and Mengert, W. F.: The Virus of Inclusion Conjunctivitis: Further Observations, Arch. Ophth. **15**:377-410 (March) 1936.

Like trachoma, inclusion blennorrhea is caused by a virus which may be a member of the psittacosis–lymphogranuloma venereum group.

Inclusion blennorrhea virus is infective for the eyes of monkeys, apes and baboons. Experimental cervical infection [51] of the female baboon has been accomplished, but it has not been possible to produce urethritis in the male baboon.[50]

Diagnosis of inclusion blennorrhea is based on clinical findings and the demonstration of typical viral inclusions in suitably stained preparations of conjunctival scrapings. Psittacosis–lymphogranuloma venereum group antibodies in low titer have been demonstrated [14c] but are of doubtful diagnostic value.

Sulfonamide therapy is highly effective in treating inclusion conjunctivitis either by topical application [52] or by oral administration.[29c] Aureomycin [33] has shown excellent results in treatment in 2 cases of inclusion conjunctivitis. Penicillin is considered to be ineffective.[27]

### HERPES SIMPLEX

The virus of herpes has been recognized as an infectious agent for many years, but little attention was paid to it until the end of the first world war, at which time Löwenstein [53] reported transmission of a virus from a human patient with herpetic keratitis to the rabbit cornea. In 1920,[54] it was shown that herpetic infection of the rabbit cornea might extend to the brain, with the production of an encephalitis. In the same year, an agent with the properties of herpes virus was isolated in a case of von Economo's encephalitis in man.[55] It has since been shown that herpes virus is not the cause of von Economo's encephalitis; in fact, no etiologic agent for this disease has been found to the present time.

Herpes virus is ectodermotropic. This statement is borne out by laboratory investigation and by the observation that human infection with the virus is limited to the skin, the mucous membranes, the eye and the central nervous system. The clinical form of disease is thought to be conditioned by whether or not the disease represents a primary attack by the virus, as well as by the presence or absence of circulating antibody, the site of infection and certain predisposing factors which tend to lower the natural resistance of the tissues.

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51. Thygeson and Mengert.[50] Braley, A. E.: Relation Between the Virus of Trachoma and the Virus of Inclusion Blennorrhea, Arch. Ophth. **22**:393-398 (Sept.) 1939.

52. Thygeson, P., and Stone, W., Jr.: The Treatment of Inclusion Conjunctivitis with Sulfathiazole Ointment, J. A. M. A. **119**:407-408 (May 30) 1942.

53. Löwenstein, A.: Aetiologische Untersuchungen über den fieberhaften Herpes, München. med. Wchnschr. **66**:769-770, 1919.

54. Doerr, R.: Sitzungsberichte 13. Jahresversammlung der Schweizerischen Augenärzte Diskussion, Klin. Monatsbl. Augenh. **65**:104, 1920.

55. Levaditi, C. and Harvier, P.: Virus de l'encéphalite léthargique, Compt. rend. Soc. de Biol. **83**:354-355, 1920.

The term herpes simplex usually refers to the recurrent form of illness characterized by one or more vesicles on the skin or, more commonly, the lips. Herpetic infection of the genitals is termed herpes genitalis. The source of virus in these recurrent attacks is probably of intrinsic origin, for it has been shown that the virus is rarely completely eliminated after infection. The clinical form of the disease is manifest when the latent virus is activated by some evoking principle such as fever, gastric disorder, vaccination or the like.

Acute herpetic stomatitis is primarily a disease of children, characterized by a systemic reaction and by vesicular eruption of the mucous membranes. It is believed to represent a first infection with the virus.[56] The disease is rarely found in infants under 6 months of age. This fact is believed to be due to the presence of circulating antibody obtained from the immune mother. Recurrent stomatitis occurs in persons who have had a previous infection with herpes. The lesions are similar to those of the acute form, but the systemic reaction is usually lacking and the infection is suppressed through the existence of a low grade immunity in the host.

The proportion of persons susceptible to herpes stomatitis is highest in childhood and progressively decreases with age, as immunity develops after an attack of herpes in clinical or subclinical form. The proportion of immune to susceptible persons in a given population varies with the socioeconomic level, a considerably higher percentage of immune persons being found in the lower strata, where poor hygienic conditions make for greater ease of passage of virus from person to person. The majority of persons are infected with herpes virus by the time they reach maturity.

Herpetic infection of the central nervous system may give rise to a severe and sometimes fatal meningoencephalitis.[57] Infection of the eye with herpes virus is common and produces a keratoconjunctivitis almost identical to that caused by the virus of epidemic keratoconjunctivitis.[58]

56. (*a*) Dodd, K.; Johnston, L. M., and Buddingh, G. J.: Herpetic Stomatitis, J. Pediat. **12**:95-102 (Jan.) 1938. (*b*) Burnet, F. M., and Williams, S. W.: Herpes Simplex: A New Point of View, M. J. Australia **1**:637-642 (April 29) 1939. (*c*) Buddingh, G. J.: Virus Stomatitis and Virus Diarrhea of Infants and Young Children, South. M. J. **39**:382-390 (May) 1946

57. Armstrong, C.: Herpes Simplex Virus Recovered from the Spinal Fluid of a Suspected Case of Lymphocytic Choriomeningitis, Pub. Health Rep. **58**:16-21 (Jan. 1) 1943. Zarafonetis, C. J. D.; Smadel, J. E.; Adams, J. W., and Haymaker, W.: Fatal Herpes Simplex Encephalitis in Man, Am. J. Path. **20**:429-445 (May) 1944. Whitman, L.; Wall, M. J., and Warren, J.: Herpes Simplex Encephalitis: A Report of Two Fatal Cases, J. A. M. A. **131**:1408-1411 (April 24) 1946.

58. Maumenee, A. E.; Hayes, G. S., and Hartman, T. L.: Isolation and Identification of the Causative Agent of Epidemic Keratoconjunctivitis (Superficial Punctate Keratitis) and Herpetic Keratoconjunctivitis, Am. J. Ophth. **28**:823-839 (Aug.) 1945.

A complication of eczema in infants, characterized by varicelliform eruption, was first described by Kaposi.[59] This entity is commonly known as Kaposi's varicelliform eruption. Considerable controversy regarding the etiology of this disease has arisen, primarily because of the confusion with the clinically similar eczema vaccinatum.[60] The first isolation of herpes virus from Kaposi's varicelliform eruption was made by Seidenberg.[61] This observation has been repeatedly confirmed.[62] It is now believed that there are at least two similar eruptions which appear on eczematous lesions. The one is caused by vaccinia and is known as eczema vaccinatum. The other is herpetic and is known as Kaposi's varicelliform eruption. It has been pointed out [62b] that in practically every case of Kaposi's varicelliform eruption there has been some preceding disease of the skin such as atopic dermatitis.

The virus of herpes is of intermediate size, having been estimated to be from 0.1 to 0.2 micron in diameter.[63] Eosinophilic inclusions, first described by Lipschütz,[64] occur within the nuclei of infected cells.

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59. Kaposi, M.: Pathology and Treatment of Diseases of the Skin for Practitioners and Students, ed. 5, translated by J. C. Johnston, New York, Wm. Wood & Co., 1895.

60. Lane, C. W., and Herold, W. C.: Kaposi's Varicelliform Eruption: Report of Five Cases, Arch. Dermat. & Syph. **50**:396-404 (Dec.) 1944.

61. Seidenberg, S.: Zur Aetiologie der Pustulosis vacciniformis acuta, Schweiz. Ztschr. f. Path. u. Bakt. **4**:398-401, 1941.

62. (*a*) Lane and Herold.[60] (*b*) Barton, R. L., and Brunsting, L. A.: Kaposi's Varicelliform Eruption: Review of the Literature and Report of Two Cases of Its Occurrence in Adults, Arch. Dermat. & Syph. **50**:99-104 (Aug.) 1944. (*c*) Lynch, F. W.; Evans, C. A.; Bolin, V. S., and Steves, R. J.: Kaposi's Varicelliform Eruption: Extensive Herpes Simplex as a Complication of Eczema, with Addendum, ibid. **51**:129-137 (Feb.) 1945. (*d*) Jaquette, W. A., Jr.; Convey, J. H., and Pillsbury, D. M.: Kaposi's Varicelliform Eruption: Studies on Etiology, Am. J. Dis. Child. **71**:45-52 (Jan.) 1946. (*e*) Lynch, F. W., and Steves, R. J.: Kaposi's Varicelliform Eruption, Arch. Dermat. & Syph. **55**:327-336 (March) 1947. (*f*) Ruchman, I.; Welsh, A. L., and Dodd, K.: Kaposi's Varicelliform Eruption: Isolation of the Virus of Herpes Simplex from the Cutaneous Lesions of Three Adults and One Infant, ibid. **56**:846-863 (Dec.) 1947.

63. Bechhold, H., and Schlesinger, M.: Die Grössenbestimmung von Herpesvirus durch Zentrifugierversuche, Ztschr. f. Hyg. u. Infektionskr. **115**:342-353, 1933. Elford, W. J.; Perdrau, J. R., and Smith, W.: The Filtration of Herpes Virus Through Graded Collodion Membranes, J. Path. & Bact. **36**:49-54 (Jan.) 1933.

64. Lipschütz, B.: Untersuchungen über die Aetiologie der Krankheiten der Herpesgruppe (Herpes zoster, Herpes genitalis, Herpes febrilis), Arch. f. Dermat. u. Syph. **136**:428-482, 1921.

The laboratory provides little help in the routine diagnosis of herpetic infection, since laboratory diagnosis involves the laborious process of isolating and identifying the infectious agent.

Rabbits, mice, guinea pigs, hamsters, cotton rats and the fertile egg are susceptible to the virus of herpes, with rabbits and mice being used most commonly for primary isolation of the virus. Rabbits given inoculation onto the scarified cornea manifest a keratoconjunctivitis, and rabbits and mice may be infected by intracerebral inoculation of virus. Inoculation on the chorioallantois of the fertile egg gives rise to the formation of plaques.

Indentification of an isolated strain of herpes virus is effected either by means of cross immunity test, with the use of mice known to be immune to established strains of herpes virus, or by serum neutralization tests in mice, known herpes immune serum being used.

Serologic diagnosis of herpes in patients involves the demonstration of a significant rise in titer of antibody during convalescence. Serum antibody is usually measured by means of the intracerebral neutralization test in mice. Since, as indicated earlier, the majority of adult persons possess neutralizing antibody to herpes at all times, this test is of little practical importance. A specific skin test for herpes, involving the intradermal injection of heated amniotic fluid from herpes-infected eggs, has recently been described.[65] Such an antigen would be necessarily limited in usefulness for diagnostic purposes because of the widespread presence of herpes antibody in so-called normal persons.

Therapeutic procedures for the treatment of herpes are nonspecific and involve the local treatment of the infected area. A number of workers have reported favorable results attending the use of successive vaccine therapy with smallpox vaccine.[66] There is no reason to recommend this procedure on a theoretic basis, and the efficacy of this treatment has not been established.

### EPIDEMIC KERATOCONJUNCTIVITIS

Epidemic keratoconjunctivitis first assumed major importance in the United States when it occurred at a Veterans Administration hospital

65. Nagler, F. P. O.: A Herpes Skin Test Reagent from Amniotic Fluid, Australian. J. Exper. Biol. & M. Sc. **24**:103-105 (June) 1946. Rose, H. M., and Molloy, E.: Cutaneous Reactions with the Virus of Herpes Simplex, J. Immunol. **56**:287-294 (July) 1947.

66. Foster, P. D., and Abshier, A. B.: Smallpox Vaccine in the Treatment of Recurrent Herpes Simplex, Arch. Dermat. & Syph. **36**:294-301 (Aug.) 1937. Grace, A. W.: Beneficial Effect of Smallpox Vaccine on Recurrent Aphthous Ulcers of Mouth and Tongue, ibid. **48**:151-152 (Aug.) 1943.

in California in 1936.[67] It later emerged as an epidemic in the shipyards and came to be known as "shipyard conjunctivitis."[68]

The viral etiology of epidemic keratoconjunctivitis was first definitely established by Sanders and Alexander in 1943.[69] These workers isolated a filterable virus which could be cultivated in tissue culture[69] and the fertile egg,[70] which was pathogenic for mice and rabbits[69] and was neutralized[69] by serum of patients convalescent from the disease.

The similarity in the clinical pictures of epidemic keratoconjunctivitis and herpetic keratoconjunctivitis stimulated investigations[58] into the relation of the two viruses. The virus of epidemic keratoconjunctivitis was shown to resemble the herpes virus in that, after a sufficient number of mouse passages, it gave rise to a keratitis in rabbits similar to experimental herpetic keratitis even to the production of the herpetic type of intranuclear inclusion bodies. A serologic relation was demonstrated by means of the serum neutralization test. Although the viruses are obviously related, they show certain differences, and it is currently believed[58] that they should be considered separate entities.

Laboratory procedures may prove helpful in establishing the diagnosis in cases of epidemic keratoconjunctivitis. However, their use should be regarded and treated as belonging to a research problem.

Convalescent serum[71] and methylene blue[58] therapy have been suggested for treatment of epidemic keratoconjunctivitis during the early illness, but the efficacy of these measures has not been proved. Aureomycin is said to have some effect if treatment is initiated before the fourth day of the disease.[33]

### REITER'S DISEASE

Reiter's disease[72] is an illness of young adult males which is characterized, in most cases, by the symptom triad of urethritis, conjunctivitis

67. Hobson, L. C.: Acute Epidemic Superficial Punctate Keratitis, Am. J. Ophth. **21**:1153-1155 (Oct.) 1938.

68. Sanders, M.: Epidemic Keratoconjunctivitis ("Shipyard Conjunctivitis"): I. Isolation of a Virus, Arch. Ophth. **28**:581-586 (Oct.) 1942.

69. Sanders, M., and Alexander, R. C.: Epidemic Keratoconjunctivitis: I. Isolation and Identification of a Filterable Virus, J. Exper. Med. **77**:71-96 (Jan.) 1943.

70. Calkins, H. E., and Bond, G. C.: Adaptation of Virus of Epidemic Keratoconjunctivitis to Development in Extra-Embryonic Fluids of Chick Embryo, Proc. Soc. Exper. Biol. & Med. **56**:46 (May) 1944.

71. Braley, A. E., and Sanders, M.: Treatment of Epidemic Keratoconjunctivitis: Preliminary Report of Ten Cases, J. A. M. A. **121**:999-1000 (March 27) 1943.

72. Reiter, H.: Ueber eine bisher unerkannte Spirochäteninfektion (Spirochaetosis arthritica), Deutsche med. Wchnschr. **42**:1535-1536, 1916. Twiss, J. R., and Douglas, A. H. R.: Reiter's Disease: A Report of Two Cases, Ann. Int. Med. **24**:1043-1051 (June) 1946. Pinck, B. D.: Reiter's Syndrome, Am. J. M. Sc. **214**:76-79 (July) 1947.

and arthritis. A fourth symptom consisting of ulcerative lesions on the skin, the mucous membranes of the mouth and the glans penis may also occur.

Although there have been numerous papers on the subject, the etiology of Reiter's disease has never been established. The possible role of pleuropneumonia-like organisms in this disease has been suggested and supported by the isolation of such organisms from the joint fluids and genital tracts of persons with this illness.[73] However, the failure to demonstrate pleuropneumonia-like organisms in the majority of cases studied suggests that other etiologic factors may be involved.

A possible viral etiology has been suggested by Dunham and associates,[74] who reported isolation of a filtrable virus in a case of Reiter's disease which gave rise to a conjunctivitis in mice after passage in the fertile egg. Further work will be necessary to establish the significance of these results because of the frequent spontaneous conjunctivitis which occurs in white mice.

The possible etiologic relation of Reiter's disease to the stomatitis and diarrhea of the newborn is of special interest. In 1946 Buddingh [56c] reported isolation of a virus from a single case of Reiter's disease which infected the cornea of the eye of a rabbit and appeared to be similar to or identical with the virus obtained in cases of infant diarrhea. The significance of this single observation has not been established, but it has opened another avenue of approach for further investigations.

It is always well for one to maintain a practical point of view when attempting to discover a new viral etiology in an old disease. Colonel Kimbrough, chief of the genitourology clinic at the Walter Reed General Hospital, expressed the opinion that certain cases of Reiter's disease are nothing more than "burned-out" gonorrhea.

### VARICELLA AND HERPES ZOSTER

Varicella and herpes zoster are caused by viruses of approximately 0.25 micron in diameter.[75] Acidophilic intranuclear inclusions are found in infected cells in both diseases.

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73. Willcox, R. R.; Findlay, G. M., and Henderson-Begg, A.: Treatment of Reiter's Syndrome by Gold Salts, Brit. M. J. **1**:483-484 (April 12) 1947. Dienes, L.; Ropes, M. W.; Smith, W. E.; Madoff, S., and Bauer, W.: Medical Progress: The Role of Pleuropneumonia-like Organisms in Genito-Urinary and Joint Diseases (Concluded), New England J. Med. **238**:563-567 (April 15) 1948.

74. Dunham, J.; Rock., J., and Belt, E.: The Isolation of a Filterable Agent Pathogenic for Mice from a Case of Reiter's Disease, J. Urol. **58**:212-215 (Sept.) 1947.

75. Taniguchi, T.; Hosokawa, M.; Kuga, S., and Masuda, Z.: The Virus of Herpes Zoster, Jap. J. Exper. Med. **12**:101-104 (Feb. 20) 1934. Nagler, F. P. O., and Rake, G.: The Use of the Electron Microscope in Diagnosis of Variola, Vaccinia and Varicella, J. Bact. **55**:45-51 (Jan.) 1948.

Successful transmission of varicella and herpes zoster viruses to rabbits and monkeys has been reported,[76] but final proof is lacking. Herpes zoster virus has been propagated in skin tissue cultured on the chorioallantois of the fertile egg.[77]

The problem of the relation of the two viruses is one of long standing, and there is disagreement in the observations and opinions of the workers. It would appear, however, that while the viruses are probably related, final elucidation of the true relation will depend on further investigation.

There is no specific therapy for these diseases, and the laboratory is of no assistance in diagnosis.

### WARTS (VERRUCAE)

It has been definitely shown that warts are caused by a filtrable virus,[78] which is presumably of small size since it will pass Berkefeld filters of all porosities. It is commonly believed that all types of warts are caused by a single virus. This conclusion is based on the observation [79] that various types of warts may coexist on the same patient and that intradermal inoculation of the human subject with genital or laryngeal wart material gives rise to plane warts.

Apparently, animal warts are not transmissible to man, but successful transmission of the virus of human laryngeal papillomas to the vaginal mucosa of a dog has been reported.[79]

An imposing list of nonspecific therapeutic measures comprised of internal medication and local treatment with heat, cold, caustics, keratolytic agents, roentgen radiation and radium has been recommended.[80]

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76. Lipschütz.[64] Rivers, T. M.: Varicella in Monkeys: Nuclear Inclusions Produced by Varicella Virus in the Testicles of Monkeys, J. Exper. Med. **45**:961-968 (June) 1927. Taniguchi, T.; Hosokawa, M.; Kuga, S.; Nakamura, F., and Matsumoto, S.: On the Virus of Chickenpox, Jap. J. Exper. Med. **10**:599-605 (Dec. 20) 1932. Eckstein, A.: Klinische und experimentelle Untersuchungen zur Frage des Varicellenencephalitis, Ztschr. f. d. ges. Neurol. u. Psychiat. **149**:176-190, 1933.

77. Goodpasture, E. W., and Anderson, K.: Infection of Human Skin, Grafted on the Chorioallantois of Chick Embryos, with the Virus of Herpes Zoster, Am. J. Path. **20**:447-455 (May) 1944.

78. Wile, U. J., and Kingery, L. B.: The Etiology of Common Warts: Preliminary Report of an Experimental Study, J. A. M. A. **73**:970-973 (Sept. 27) 1919. Kingery, L. B.: The Etiology of Common Warts: Their Production in the Second Generation, ibid. **76**:440-442 (Feb. 12) 1921. Findlay, G. M., in Browning, C. H., and others: A System of Bacteriology in Relation to Medicine, London, His Majesty's Stationery Office, 1930, vol. 7, chap. 18, p. 255.

79. van Rooyen, C. E., and Rhodes, A. J.: Virus Diseases of Man, ed. 2, New York, Thos. Nelson & Sons, 1948, chap. 15, p. 152.

80. Rulison, R. H.: Warts: A Statistical Study of Nine Hundred and Twenty-One Cases, Arch. Dermat. & Syph. **46**:66-81 (July) 1942. Burrows, A.: The Treatment of Warts, Brit. J. Dermat. & Syph. **55**:60-65 (March) 1943.

Successful vaccine therapy using wart extract has been claimed.[81] There is some doubt whether any of these therapeutic measures are any more efficacious than the "spunk water" and "dead cats" so zealously recommended by Tom Sawyer and Huckleberry Finn.[82] Indeed, remarkable cures of warts in many instances have attended the use of psychosuggestion, and, because of this factor, it is difficult to assay the effectiveness of the various therapeutic measures which have been employed.

More recently, remarkable cures of venereal warts have been claimed to follow application of resin of podophyllum,[83] a resinous material obtained from the roots of the May apple, or mandrake. Unfortunately, resin of podophyllum has proved ineffective [84] in the treatment of verruca vulgaris, but succesful therapy of plantar warts [85] has been reported following application of the substance by a special technic.

### MOLLUSCUM CONTAGIOSUM

Molluscum contagiosum is an infectious disease caused by a filtrable virus.[86] The cytoplasm of cells infected with this virus can be readily shown to contain a large, hyaline, acidophilic, granular inclusion body which is commonly referred to as the molluscum body. The molluscum body [87] has been shown to be composed of a mass of elementary bodies embedded in a sticky substance which is enclosed within a limiting membrane. The elementary bodies are 0.25 micron in diameter [88] and are believed to represent the infectious particle.

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81. Biberstein, H.: Immunization Therapy of Warts, Arch. Dermat. & Syph. **50**:12-22 (July) 1944.

82. Twain, M.: The Adventures of Tom Sawyer, in Mark Twain's Works, New York, Harper & Brothers, 1906, vol. 12, p. 72.

83. Culp, O. S., and Kaplan, I. W.: Condylomata Acuminata: Two Hundred Cases Treated with Podophyllin, Ann. Surg. **120**:251-256 (Aug.) 1944. Macgregor, J. V.: Treatment of Soft Warts with Podophyllin, Brit. M. J. **1**:593-594 (April 28) 1945. Sullivan, M., and King, L. S.: Effects of Resin of Podophyllum on Normal Skin, Condylomata Acuminata and Verrucae Vulgares, Arch. Dermat. & Syph. **56**:30-47 (July) 1947.

84. Frank S. B., and Cohen, W. S.: Failure of Resin of Podophyllum in the Treatment of Verruca Vulgaris, Arch. Dermat. & Syph. **56**:109-110 (July) 1947.

85. Kurtin, A., and Yontef, R.: Podophyllum Therapy for Plantar Warts, Arch. Dermat. & Syph. **57**:395-396 (March) 1948.

86. Juliusberg, M.: Zur Kenntnis des Virus des Molluscum contagiosum des Menschen, Deutsche. med. Wchnschr. **31**:1598-1599, 1905.

87. Goodpasture, E. W., and King, H.: A Cytologic Study of Molluscum Contagiosum, Am. J. Path. **3**:385-394 (July) 1927. Goodpasture, E. W., and Woodruff, C. E.: A Comparison of the Inclusion Bodies of Fowl-Pox and Molluscum Contagiosum, ibid. **7**:1-8 (Jan.) 1931. van Rooyen, C. E.: The Micromanipulation and Microdissection of the Molluscum Contagiosum Inclusion Body, J. Path. & Bact. **46**:425-436 (May) 1938.

88. Lipschütz, B.: Zur Kenntnis des Molluscum contagiosum, Wien. klin. Wchnschr. **20**:253-254, 1907.

Laboratory diagnosis of infection with this virus is readily accomplished by the demonstration under the microscope of molluscum bodies in the exudate expressed from the lesions. The inclusion bodies are made apparent by digestion with potassium hydroxide or by staining with strong iodine solution U.S.P. (Lugol's iodine) or brilliant cresyl blue.[89]

Treatment usually consists of the local destruction of infected cells with phenol or of curettage. Successful treatment with the sulfonamides has been reported [90] and has been recommended in cases in which the lesions are numerous.

### SMALLPOX (VARIOLA) AND VACCINIA

Extensive investigations of the viruses of smallpox and vaccinia and the related pox diseases of animals have provided a vast and illuminating literature on the subject. The results of these researches have been thoroughly reviewed [91] and, except for certain special considerations, will not be discussed here.

The laboratory may serve a useful purpose in the establishment of the diagnosis of infection with these viruses. Typical elementary bodies may be seen in materials from vesicles and early eruptive lesions when suitably stained preparations are observed under the ordinary microscope. Isolation of the virus from early or late cutaneous lesions may be accomplished by inoculation of the chorioallantois of the fertile egg, with the formation of opacities in the membrane. Immunologic diagnosis may be accomplished by means of the complement fixation test or the flocculation test, known antiviral serum and antigens prepared from the lesions or the crusts being used. Tests for antibody in the patient's serum may prove useful in the establishment of a retrospective diagnosis. This aim is accomplished by demonstration of a rise in titer of serum antibody during convalescence by means of the neutralization, complement fixation or flocculation test.

In the course of investigations on influenza virus, Hirst [92] in 1941 noted that allantoic fluid from infected eggs brought about an agglutination of red blood cells. This observation, commonly referred to as the Hirst phenomenon, has been intensively studied and extended to a num-

89. van Rooyen and Rhodes,[79] chap. 14, p. 148.

90. Hill, W. R., and Downing, J. G.: Molluscum Contagiosum Cured with Sulfapyridine, Arch. Dermat. & Syph. **46**:139-140 (July) 1942. Laymon, C. W.: Molluscum Contagiosum Treated with Sulfadiazine, ibid. **53**:643 (June) 1946.

91. van Rooyen and Rhodes,[79] chaps. 26-35, pp. 282-429. Smadel, J. E., in Rivers, T. M.: Viral and Rickettsial Infections of Man, Philadelphia, J. P. Lippincott Company, 1948, chap. 15, pp. 314-336.

92. Hirst, G. K.: The Agglutination of Red Cells by Allantoic Fluid of Chick Embryos Infected with Influenza Virus, Science **94**:22-23 (July 4) 1941.

ber of other viruses, including those of smallpox and vaccinia.[93] Emulsions of the chorioallantoic membranes of fertile eggs infected with the last-mentioned viruses were shown to agglutinate the red blood cells of a number of mammals and birds. It was demonstrated, further, that the hemagglutination was inhibited by appropriate immune serums of human or animal origin.

The therapeutic effectiveness of antibacterial drugs in smallpox apparently is limited to the control of secondary bacterial invaders. Certain crude penicillins have been shown to inactivate the virus of vaccinia,[94] but the effect was found to be due to some impurity present in the crude material, since purified penicillin was ineffective. The sulfonamides and streptomycin are without effect on this virus.[95]

### MILKER'S NODULES

Milker's nodules [96] is usually a local infectious disease of the hands characterized by the formation of red papules which become bluish red nodules. The disease occurs among milkers, animal tenders and slaughterhouse workers following contact with the lesions on the udders of infected cows.

Most workers favor a viral etiology, and it is currently believed that the disease is caused by one of the pox group of viruses which is related to vaccinia virus. The disease is self limited and resolves itself spontaneously.

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93. Nagler, F. P. O.: Application of Hirst's Phenomenon to Titration of Vaccinia Virus and Vaccinia Immune Serum, M. J. Australia **1**:281-283 (March 7) 1942. North, E. A.: A Study of the Immunological Reactions of the Variola and Vaccinia Viruses Grown in the Developing Egg, Australian J. Exper. Biol. & M. Sc. **22**:105-109 (June) 1944. Burnet, F. M., and Stone, J. D.: The Haemagglutinins of Vaccinia and Ectromelia Viruses, ibid. **24**:1-8 (March) 1946.

94. Groupe, V., and Rake, G.: Studies on Chemotherapy of the Pox Viruses: I. The Effect of Commercial Penicillin and Other Selected Substances on Canary Pox Viruses, J. Immunol. **57**:17-29 (Sept.) 1947. Gohar, M. A., and Bashatli, A.: The Effect of Penicillin on the Vaccinia Virus, J. Trop. Med. & Hyg. **49**:115-116 (Dec.) 1946.

95. Kolmer, J. A., and Brown, H.: Failure of Sulfanilamide in Treatment of Experimental Vaccinia in Rabbits, Proc. Soc. Exper. Biol. & Med. **48**:138-140 (Oct.) 1941. Andrewes, C. H.; King. H., and van den Ende, M.: Chemotherapeutic Experiments with the Viruses of Influenza A, Lyphogranuloma Venereum and Vaccinia, J. Path. & Bact. **55**:173-181 (April) 1943. Kolmer, J. A., and Rule, A. M.: Failure of Penicillin and Streptomycin in the Prophylaxis and Treatment of Experimental Vaccinia of Rabbits, Proc. Soc. Exper. Biol. & Med. **63**:376-377 (Nov.) 1946. Thompson, R. L.: The Effect of Metabolites, Metabolite Antagonists and Enzyme-Inhibitors on the Growth of Vaccinia Virus in Maitland Type of Tissue Cultures, J. Immunol. **55**:345-352 (April) 1947.

96. Becker, F. T.: Milker's Nodules, J. A. M. A. **115**:2140-2144 (Dec. 21) 1940.

### ECTHYMA CONTAGIOSUM (OVINE POSTULAR DERMATITIS)

Ecthyma contagiosum is an infectious viral disease of sheep and goats characterized by the appearance of vesiculopustular lesions on the lips and adjacent tissues and the non-wool-bearing parts of the body. The infection is transmissible to man [97] and occurs in persons handling infected sheep. In man, the disease is characterized by the formation of papules and papulovesicular and pustular lesions on the hands and face.

Although there are relatively few cases of human infection on record, Kingery and Dahl [97a] have presented evidence which would indicate that ecthyma contagiosum in man is probably not uncommon in the sheep-raising areas of the United States, and they have concluded that the disease should be recognized as a dermatosis with greater frequency and wider geographic distribution than previous investigations have indicated.

The causative agent appears to be distinct [97b] from the viruses of smallpox, vaccinia and sheep pox, and it is believed [97a] that a lasting immunity may follow a single infection. Laboratory diagnosis is of a purely research nature and involves the attempt to isolate the virus in sheep. The disease is self limited and resolves itself with the mildest symptomatic treatment.

### FOOT-AND-MOUTH DISEASE

Foot-and-mouth disease is a devastating infectious disease affecting cattle primarily but also goats, sheep and pigs. The disease in these animals is characterized by fever and the presence of vesicles in the mouth and on the lips and feet. The disease is occasionally transmitted to man.

The causal agent is one of the smallest viruses, having a diameter of about 10 to 20 millimicrons.[98] There are three immunologically distinct strains.[99] The disease is self limited in man, and there is no specific treatment.

This virus infection is now raging among cattle in Mexico. The governments of the United States and Mexico are currently engaged in

97. (*a*) Kingery, L. B., and Dahl, J.: Ecthyma Contagiosum in Man, Arch. Dermat. & Syph. **51**:359-364 (June) 1945. (*b*) Carne, H. R.; Wickham, N.; Whitten, W. K., and Lockley, R. P.: Infection of Man by the Virus of Contagious Pustular Dermatitis of Sheep, Australian J. Sc. **9**:73-74 (Oct.) 1946.

98. Elford, W. J., and Galloway, I. A.: Centrifugation Studies: III. The Viruses of Foot-and-Mouth Disease and Vesicular Stomatitis, Brit. J. Exper. Path. **18**:155-161 (April) 1937.

99. Waldmann, O., and Trautwein, K.: Experimentelle Untersuchungen über die Pluralität des Maul-und-Klauensuchevirus, Berl. tierärztl. Wchnschr. **42**:569-571, 1926.

an intensive campaign [100] to eradicate the disease, but it is problematic whether they will succeed. If they fail, it will mean a loss of hundreds of millions of dollars to the American and Mexican cattlemen. The virus of foot-and-mouth disease does not occur in the United States at the present time, and its importation, even for research, is prohibited. Congress has, however, recently authorized the building of a research institute for the study of this disease on some island adjacent to the mainland.[101]

### PRETIBIAL FEVER (FORT BRAGG FEVER)

Pretibial fever was first described as a clinical entity in 1943 by Daniels and Grennan,[102] who investigated an outbreak of the disease among soldiers at Fort Bragg, N. C. The disease was characterized by fever, headache, malaise, palpable spleen and an unusual eruption consisting of raised, erythematous blotches of irregular outline occurring on and usually limited to the pretibial areas. In 2 cases, however, the rash was diffusely distributed over the entire body.

Attempts to isolate the causative organism resulted in failure until Tatlock in 1947 [103] isolated an agent, presumably viral, from the blood of a patient by means of the inoculation of guinea pigs. The agent proved infective for guinea pigs, rabbits, hamsters and fertile eggs. After prolonged passage in guinea pigs and embryonated eggs, the virus was able to induce typical Fort Bragg fever in some inoculated human beings, but the majority of these persons exhibited only fever for one to three days. An attempt to filter the virus through a single Seitz pad resulted in failure, but successful passage through a Corning fritted glass filter (U.F.) which held back Staphylococcus albus organisms was accomplished. Further investigations will be necessary to establish the proof for viral etiology.

There are no simple laboratory diagnostic procedures available. The disease is self limited. There is no specific therapy.

### DENGUE (BREAKBONE FEVER)

Dengue is an infectious febrile disease characterized by fever, pain, prostration, lymphadenopathy, leukopenia and scarlatiniform or maculo-

100. Developments in the Campaign Against Foot-and-Mouth Disease in Mexico, Report no. 18, United States Department of Agriculture, Bureau of Animal Industry, Feb. 7, 1949.

101. Public Law 496, 80th Congress (Ch. 229-2D Session) S. 2038, approved April 24, 1948.

102. Daniels, W. B., and Grennan, H. A.: Pretibial Fever: An Obscure Disease, J. A. M. A. **122**:361-365 (June 5) 1943.

103. Tatlock, H.: Studies on a Virus from a Patient with Fort Bragg Fever (Pretibial Fever), J. Clin. Investigation **26**:287-297 (March) 1947.

papular rash. Another type of eruption consisting of small petechiae may occur on or shortly after the last day of fever. Great epidemics of this disease have occurred in the United States.[104]

The disease is caused by a filtrable virus,[105] about 17 to 25 millimicrons[106] in diameter and is transmitted by Aedes mosquitoes.

Extensive investigations of dengue were made by Sabin[106] and his associates during World War II. Studies to determine the host range of the virus revealed that inapparent infections could be established in monkeys, but all other laboratory animals proved refractory. These workers were able, however, to adapt the virus to white mice by serial intracerebral passage. The mouse-adapted virus proved infective for fertile eggs, and monkeys inoculated by the intracerebral route acquired fever and neutralizing antibodies. Of greatest significance was the loss of capacity of the mouse-adapted virus to produce severe illness in man, which made possible the preparation of an attenuated active viral vaccine[107] against dengue. There were at least three distinct immunologic types of virus.

A satisfactory neutralization test is available for diagnosis of infection caused by the dengue virus. Treatment is symptomatic; there is no specific therapy.

### MEASLES (MORBILLI)

Measles is caused by a filtrable virus which is infectious for the monkey[108] and which can be cultivated in tissue culture[109] and in the embryonated egg.[110] It has been reported that successive passage of measles virus in fertile eggs resulted in an alteration of the virus to

104. Chandler, A. C., and Rice, L.: Observations on the Etiology of Dengue Fever, Am. J. Trop. Med. **3**:233-262 (May) 1923. Armstrong, C.: Dengue Fever, Pub. Health Rep. **38**:1750-1784 (Aug. 3) 1923. Griffitts, T. D. H., and Hanson, H.: Significance of Epidemic of Dengue, J. A. M. A. **107**:1107-1110 (Oct. 3) 1936.

105. Ashburn, P. M., and Craig, C. F.: Experimental Investigations Regarding the Etiology of Dengue Fever, J. Infect. Dis. **4**:440-475, 1907.

106. Sabin, A. H.; in Rivers, T. M.: Viral and Rickettsial Infections of Man, Philadelphia, J. B. Lippincott Company, 1948, chap. 30, pp. 445-453.

107. Sabin, A. B., and Schlesinger, R. W.: Production of Immunity to Dengue with Virus Modified by Propagation in Mice, Science **101**:640-642 (June 22) 1945.

108. Goldberger, J., and Anderson, J. F.: The Nature of the Virus of Measles, J. A. M. A. **57**:971-972 (Sept. 16) 1911.

109. Plotz, H.: Culture "in vitro" du virus de la rougeole, Bull. Acad. de méd. Paris **119**:598-601 (May 31) 1938. Rake, G.; Shaffer, M. F., and Jones, H. P.: Studies on Measles: III. The Use of Tissue Culture in Propagation of Measles Virus, J. Infect. Dis. **69**:65-69 (July-Aug.) 1941.

110. Rake, G., and Shaffer, M. F.: Propagation of the Agent of Measles in the Fertile Hen's Egg, Nature **144**:672-673 (Oct. 14) 1939.

bring about only a modified form of the disease [111] on the inoculation of the human host. Infection with the modified egg passage virus gave rise to an increased resistance [112] to natural infection with measles or to challenge inoculation with virus from human material.

Chemotherapeutic agents are ineffective in measles uncomplicated by bacterial infection, but biologic therapy involving the use of immune serum has found widespread acceptance as a seroprophylactic measure. It was shown that convalescent measles serum [113] or adult serum [114] prevented infection in contacts if given early and induced a mild abortive attack [115] when administered later in the incubation period. This observation gave rise to the current practice of administering serum at the appropriate interval following exposure to induce a mild infection without preventing the development of a lasting immunity. The gamma globulin fraction [116] of human plasma has also proved highly effective as a prophylactic measure [117] and will very likely be the material of choice in the future.

The virus laboratory is of no assistance in the diagnosis of measles.

## RUBELLA (GERMAN MEASLES)

Viral etiology in rubella was first established by Hiro and Tasaka in 1938 [118] through transmission of the disease to children by the use of

111. Stokes, J. Jr.; O'Neil, G. C.; Shaffer, M. F.; Rake, G., and Maris, E. P.: Studies on Measles: IV. Results Following Inoculation of Children with Egg-Passage Measles Virus, J. Pediat. **22**:1-16 (Jan.) 1943.

112. Stokes, O'Neil, Shaffer, Rake and Maris.[111] Maris, E. P.; Rake, G.; Stokes, J. Jr.; Shaffer, M. F., and O'Neil, G. C.: Studies on Measles: V. The Results of Chance and Planned Exposure to Unmodified Measles Virus in Children Previously Inoculated with Egg-Passage Measles, Virus, J. Pediat. **22**:17-29 (Jan.) 1943.

113. Nicolle, C., and Conseil, E.: Pouvoir préventif du sérum d' un malade convalescent de rougeole, Bull. et mém. Soc. méd. d. hôp. de Paris **42**:336-338, 1918.

114. Rietschel, P.: Zur Masernprophylaxe nach Degkwitz, Ztschr. f. Kinderh. **29**:127-132 (June) 1921.

115. Debré, R., and Ravina, J.: La rougeole modifée par l'injection préventive de sérum de convalescent, Bull. et mém. Soc. méd. d. hôp. de Paris **47**:226-237 (Feb. 9) 1923.

116. Cohn, E. J.; Oncley, J. L.; Strong, L. E.; Hughes, W. L., Jr., and Armstrong, S. H., Jr.; Chemical, Clinical and Immunological Studies on the Products of Human Plasma Fractionation: I. The Characterization of the Protein Fractions of Human Plasma, J. Clin. Investigation **23**:417-432 (July) 1944.

117. Stokes, J., Jr.; Maris, E. P., and Gellis, S. S.: Chemical, Clinical and Immunological Studies on the Products of Human Plasma Fractionation: XI. The Use of Concentrated Normal Human Serum Gamma Globulin (Human Immune Serum Globulin) in the Prophylaxis and Treatment of Measles, J. Clin. Investigation **23**:531-540 (July) 1944. Janeway, C.: Use of Concentrated Human Serum and Globulin in the Prevention and Attenuation of Measles: I. Plasma Fractionation, Bull. New York Acad. Med. **21**:202-222 (April) 1945.

118. Hiro, Y., and Tasaka, L.: Die Röteln sind eine Viruskrankheit, Monatsschr. f. Kinderh. **76**:328-332, 1938.

filtered nasal washings. Successful passage to monkeys [119] and cultivation on the chorioallantois of the fertile egg [119] have also been accomplished. No indication of cross immunity between rubella and measles has been demonstrable.[119]

Chemotherapy is of no use in rubella. Presumptive evidence of the effectiveness of immune serum in preventing rubella has been reported.[120] No preventive measures are warranted, however, in rubella except in very unusual circumstances. Indeed, all female children should have had rubella before puberty because of the danger of development of congenital abnormalities in the fetus if the pregnant woman contracts the disease, especially during the first trimester.

The laboratory is of no use in the diagnosis of rubella.

### PEMPHIGUS

The etiology of pemphigus has not been established, but it is believed by most workers at the present time that the disease is caused by some factor or factors giving rise to disturbances in metabolism [121] which effect a reduction of sodium, calcium, chloride and protein in the blood stream. It has been pointed out [122] that these metabolic disturbances, except for the change in protein content, may be found in adrenal insufficiency, and, indeed, administration of adrenal preparations has been reported beneficial [123] in treating this disease in certain instances.

A theory of infection was stated by other workers. Welsh [124] expressed the belief that a streptococcus found in association with the

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119. Habel, K.: Transmission of Rubella to Macacus Mulatta Monkeys, Pub. Health Rep. **57**:1126-1139 (July 31) 1942.

120. Barenberg, L. H.; Levy, W.; Greenstein, N. M., and Greenberg, B.: Prophylactic Use of Human Serum Against Contagion in a Pediatric Ward: Further Observations with Special Reference to Measles and Rubella, Am. J. Dis. Child. **63**:1101-1109 (June) 1942.

121. (*a*) Goldman, A.; Markham, M. J., and Schaffer, A. I.: Clinical Report of the Treatment of a Case of Pemphigus with Desoxycorticotestosterone Acetate, J. Clin. Endocrinol. **2**:343-344 (May) 1942. (*b*) Lever, W. F., and Talbott, J. H.: Pemphigus: A Further Report on Chemical Studies of the Blood Stream and Treatment with Adrenocortical Extract, Dihydrotachysterol or Vitamin D, New England J. Med. **231**:44-51 (July 13) 1944.

122. Goldman, Markham and Schaffer.[121a] Kuhn, B. H., and Iverson, L.: Pemphigus Vulgaris: A Clinicoanatomic Study, Arch. Dermat. & Syph. **57**:891-899 (May) 1948.

123. Goldman, Markham and Schaffer.[121a] Lever and Talbott.[121b] Goldzieher, J. W.: The Adrenal Glands in Pemphigus Vulgaris: A Report of a Case, Arch. Dermat. & Syph. **53**:42-44 (Jan.) 1946.

124. (*a*) Welsh, A. L.: Specificity of a Streptococcus Isolated from Patients with Pemphigus, Arch. Dermat. & Syph. **30**:611-630 (Nov.) 1934; (*b*) Specificity of Streptococci Isolated from Patients with Skin Diseases: Studies on Pemphigus, Dermatitis Herpetiformis, Lupus Erythematosus, Erythema Multiforme; I. Pemphigus, J. Invest. Dermat. **7**:7-42 (Feb.) 1946. (*c*) A Diagnostic Test for

disease is of etiologic significance. Other workers [125] suggested a viral etiology, their view being based on the isolation of neurotropic viruses through inoculation of rabbits and mice with suspected materials from patients with pemphigus. Markham and Engman,[126] on the other hand, in an extensive search for a viral agent in pemphigus, were not able to repeat the work of those who reported isolation of a virus and concluded that there is insufficient evidence at the present time to justify the theory that pemphigus is caused by a virus.

A vast array of medicaments has been recommended for treating pemphigus, but the number alone indicates that probably none is of appreciable effectiveness.

### DERMATITIS HERPETIFORMS (DUHRING'S DISEASE)

As with pemphigus, the etiology of dermatitis herpetiformis has not been established. Most workers favor an etiology involving allergic sensitization.[127] A filtrable virus [128] etiology in dermatitis herpetiformis has been suggested by a number of workers, but proof is still lacking.

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Distinguishing Pemphigus, Dermatitis Herpetiformis, Disseminate Lupus Erythematosus and Erythema Multiforme Exudativum, ibid. **11**:19-48 (July) 1948.

125. (*a*) Urbach, E., and Wolfram, S.: The Virus of Pemphigus and Dermatitis Herpetiformis, Arch. Dermat. & Syph. **33**:788-806 (May) 1936. (*b*) Dostrovsky, A.; Gurevitch, I., and Ungar, H.: On the Question of the Aetiology of Pemphigus Vulgaris and Dermatitis Herpetiformis (Duhring's Disease): A Clinical Experimental Study, Brit. J. Dermat. & Syph. **50**:412-435 (Aug.-Sept.) 1938. (*c*) Grace, A. W., and Suskind, F. H.: An Agent, Transmissible to Mice, Obtained During a Study of Pemphigus Vulgaris, Proc. Soc. Exper. Biol. & Med. **37**:324-326 (Nov.) 1937. (*d*) An Investigation of the Etiology of Pemphigus Vulgaris: The Isolation of a Transmissible Agent from a Fourth Case of the Disease, J. Invest. Dermat. **2**:1-13 (Feb.) 1939.

126. Markham, F. S., and Engman, M. F., Jr.: An Inquiry Into the Cause of Pemphigus: Is It a Virus Disease? Arch. Dermat. & Syph. **41**:78-86 (Jan.) 1940.

127. Welsh.[124c] Bernhardt, R.: Weitere Beiträge zur Aetiologie des Pemphigus und der Duhringschen Krankheit, Arch. f. Dermat. u. Syph. **171**:536-555, 1935. Peck, S. M., in discussion on Kampf, M. B.: Dermatitis Herpetiformis, Arch. Dermat. & Syph. **38**:673 (Oct.) 1938. Callaway, J. L., and Sternberg, T. H.: Bacterial Allergy: An Etiologic Factor in Dermatitis Herpetiformis, ibid. **43**:956-961 (June) 1941. Swartz, J. H., and Lever, W. F.: Dermatitis Herpetiformis: Immunologic and Therapeutic Considerations, ibid. **47**:680-693 (May) 1943. Welsh, A. L.: Specificity of Streptococci Isolated from Patients with Skin Diseases: Studies on Pemphigus, Dermatitis Herpetiformis, Lupus Erythematosus and Erythema Multiforme; II. Dermatitis Herpetiformis, J. Invest. Dermat. **10**:231-248 (April) 1948.

128. Urbach and Wolfram.[125a] Dostrovsky, Gurevitch and Ungar.[125b] Werth, J.: Nachweis von Viruselementarkorperchen bei Dermatitis Herpetiformis Duhring, Arch. Ges. Virusforsch. **2**:194-204, 1941.

## CONCLUSIONS

In conclusion, let me say that, while tremendous advances have been made in our knowledge of the viruses in general, the development of suitable means for laboratory diagnosis and for chemotherapy is still in its infancy. Except for the viruses of the psittacosis–lymphogranuloma venereum group, specific chemotherapeutic measures have not been developed at the present time. Likewise, few serologic procedures of practical value in diagnosis of infection by the viruses discussed in this paper have been developed except in the case of the viruses of the psittacosis–lymphogranuloma venereum group. It should be kept in mind that any attempt to isolate a virus in a case of infection with any of the viruses which have been discussed is essentially a research problem and should be approached from this perspective.

# HORMONAL THERAPY OF ACNE VULGARIS IN THE FEMALE

## A Clinical Attempt at Its Evaluation

WILLIAM H. GOECKERMAN, M.D.
LOS ANGELES

MOST dermatologists, including me, have felt that the endocrine glands must be a determining factor in common acne, if for no other reason than its usual association with the adolescent years. While some beneficent results have been reported from treatment with present day hormones, on the whole dermatologists have been skeptical of their value. This viewpoint is well illustrated by a recent symposium, in which a number of dermatologists expressed themselves as follows:

1. "Hormonal therapy of little value"
2. "Hormonal therapy of little value except when specifically indicated by symptoms other than acne and by laboratory tests"
3. "Not able to evaluate hormonal therapy definitely. Where used results not followed long enough to be convincing. Impression that they are of no value"
4. "Never used hormones"
5. "Thyroid extract with diet of great value"
6. "Only of value in women who have associated dysmenorrhea or amenorrhea"

My opinion has been for many years that if the proper hormonal preparation could be obtained it should beneficially affect the process in acne. I therefore experimented somewhat with desoxycorticosterone and antuitrin® (unfractionated anterior pituitary extract), only to be disappointed with these preparations. In 1940 I decided to treat all female patients with acne with estrogens, hoping that eventually enough material of the right type would emerge to warrant some deductions.

### METHOD EMPLOYED

The aim of this study was not to find a short cut for the treatment of acne but rather to determine, if possible, whether the estrogens are of any value in its treatment. Both the natural, in the form of estrone derived from mare's urine, and the synthetic preparations, in the form of estradiol and diethylstilbestrol, were administered, sometimes individually and sometimes in combination. Initial doses were small but continuous. In exceptional cases doses were fairly large. At no time was the patient permitted to become uncomfortable. When symptoms of any kind suggestive of abnormal activity arose, the preparation was immediately

Read at the Sixty-Eighth Annual Meeting of the American Dermatological Association, Inc., San Diego, Calif., April 27, 1948.

reduced in dose or temporarily discontinued. The dose was never routinized but adjusted to the requirements of the individual. When the importance of this measure was first recognized the discovery came as somewhat of a surprise. After several visits, with careful observation of the general clinical and cutaneous picture of the patient, the optimal dose could be determined fairly well. As a control, possibly not a very good one, male patients were at first treated with testosterone and methyltestosterone. This part of the study soon proved unsatisfactory, chiefly because of inadequate cooperation.

Since there have been some favorable comments on the value of vitamin A in the treatment of acne, the male patients were subsequently given large doses of a preparation containing this vitamin, again serving as a control, as it were. Cooperation then was very good, sufficiently at least to establish the lack of value of vitamin A as contrasted with the value of the estrogens in the female patients.

When this study of estrogens was begun, local manipulation of the comedos was still employed; this method was later discarded entirely. Diet was discussed only in order for me to be sure that there were no gross errors. In most instances only an indifferent lotion was used. While roentgen irradiation was used sparingly it could not be discarded entirely.

It would have been desirable to follow this study by bioassay of the urinary hormones of the male as well as of the female. But this was out of the question, for several reasons.

## REPORT OF CASES

Although estrogens were given in about double the number, 26 cases which, after critical sifting, permitted an opinion as to the therapeutic value of estrogens, emerged over a period of about eight years. In order to illustrate on what type of case my observations are based, I shall report a few cases in detail.

CASE 1.—J. M., aged 16, was first seen by me in the fall of 1942. At that time full appreciation of the estrogens was not established, and they were not given to this patient then. She was given the usual treatment, including 37 r of roentgen irradiation at about weekly intervals for a total of fourteen treatments. There was fair improvement, but for some reason treatment was discontinued. The patient returned in 1947, four years later, with the acne in about the same condition as it had been in 1942. She was then given estrogens by mouth and a few roentgen ray treatments of 37 r each. Response was prompt, with complete disappearance of the eruption in six weeks. The patient, was then 21, and it may be argued that nature had come to the rescue. This theory may be true in part, but the response to treatment was so prompt that the explanation is unlikely.

CASE 2.—A. D. was first seen by me in 1944, when she was 18, with a very severe pustular type of acne. She had received competent treatment, including systematic roentgen irradiation to the accepted limit, elsewhere. The eruption had largely cleared up with roentgen therapy but recurred promptly. She was given estrogens by mouth and intramuscularly. Aside from this therapy she was given an indifferent preparation applied locally and staphylococcus toxoid subcutaneously, the latter intended for the pustular element. Response was prompt and satisfactory. The patient was seen again after an interval of two years, and there had been no recurrence. This case was so severe even after much roentgen therapy that the prompt response was hardly accidental.

CASE 3.—P. K. was first seen by me in 1947 at the age of 24. She had been treated elsewhere with repeated courses of roentgen irradiation and other conventional measures since the age of 17. She had received treatment for about a year just before I saw her. At her first visit she presented many deep-seated acne pustules and much scarring as the result of acne of the face, chest and back. She was immediately given rather large doses of estrogens by mouth and intramuscularly. Response was rather slow but symptomatically very satisfactory. The treatments have been too recent for me to determine how permanent the result will be. Since there was no other treatment, the result in so persistent and severe a case can probably be attributed to the estrogens.

CASE 4.—C. D. was first seen by me at the age of 21, in 1942. She still had an unusually severe deep-seated pustular type of acne involving very extensively the usual acne areas. She was a somewhat temperamental, wealthy person. Efforts to treat the disease had been begun years ago by well known specialists in New York city. Although I could not determine just how much roentgen irradiation the patient had received prior to consulting me, it had been given under the direction of several well known men, and the patient had been told that she should have no more roentgen irradiation for at least two years. Peeling and diet and all the usual procedures had been given a prolonged trial without success. I made a short attempt at doing something in 1942 but was not as yet sufficiently familiar with the use of estrogens in treatment of acne to take a positive stand. So I soon lost sight of the patient and she tried, somewhere, treatment with thyroid extract and diet, whether conscientiously or not being undetermined. Subsequently she returned to New York city and was evidently given another full course of roentgen therapy under competent direction. All this treatment seemingly gave no appreciable benefit. She returned in February 1947, not because she hoped for much but evidently to discuss any possible new measures. She was hysterical and very skeptical about anything I told her. But by this time my experience with treatment with estrogens had grown to such a degree that I gave almost a positive promise to cure if she persevered. So finally she started systematically to take the estrogens by mouth and intramuscularly. The dose at first was fairly large, but, as soon as symptoms of a disagreeable nature appeared, it was reduced and a moderate dose continued; at no time was any menstrual disturbance permitted to continue. In fact, the patient was of the type that would probably have objected strenuously to any disagreeable effects. Improvement could be seen at once; lesions slowly but definitely became less, so that, after ten months, when the patient was 27, the skin was clear. No other treatment was given except a placebo. This seemed indicated because of the patient's hysterical personality.

## COMMENT

Twenty-six cases were selected from the entire number in which treatment with estrogens was given because the course of events seemed such that they warranted definite conclusions. A carefully conducted bioassay of the urine for estrogens and androgenic material would have been of interest, especially if the tests could have been repeated after the estrogens had been administered for some time. In the early part of the study a test was made on 2 patients, but the tests are expensive and I could not procure a subsequent test since the acne had responded well. Later I learned that for quantitative purposes these tests are at

present unreliable. Lawrence and Werthessen [1] reported such a systematic study of acne in the female. These authors found a significant decrease in estrogen, with no increase in androgenic material but a significant increase in ratio as contrasted with the observations on the average person. It is a well known fact that acne may be produced in the female by the administration of testosterone, in some cases in rather moderate amounts. Such observations suggest that in acne of the female there might be an inadequate supply of estrogens to establish a proper balance with the male hormone in the various cells of the body, including the skin. In this connection it should be recalled that estrogenic material is found, not only in the ovaries, but in most structures of the body, although in lesser quantities.

The attempted control with the administration of testosterone to male patients proved unsatisfactory. Observations on the moderate number of persons to whom the hormone was given in reasonably adequate amounts seemed to indicate its lack of value, but a final opinion is not justified. On the contrary, vitamin A was given in large doses to a sufficient number and in adequate amounts, again as a control, to suggest strongly an absence of therapeutic value as contrasted with the effect of the estrogens in treatment of the female patients.

The therapeutic mechanism involved needs further investigation, but this study suggests that acne may be a manifestation of inadequate secretion of estrogens in the female. It does not signify that the older measures should be discarded, since some time is evidently required before the cells of the body, including those of the skin, can be adequately satisfied artificially. Probably the ideal experiment could be performed with an intelligent person fully cooperative over a considerable period of time, without any other treatment.

It is of decided theoretic interest that estrogens are derivatives of and related to the carcinogenic hydrocarbons. But there is no satisfactory evidence that estrogens used therapeuticaly have initiated cancer in the human being. Grollman [2] said that, if one can judge from the doses required to produce cancer experimentally, it would require about 1,000,000 international units daily, with administration begun before puberty and continued for several decades, to induce cancer in the human organism.

## SUMMARY AND CONCLUSIONS

Over a period of about eight years in which estrogens were given, at one time or another 26 cases emerged which seemed after critical sifting

1. Lawrence, C. H., and Werthessen, N. T.: The Endocrine Dyscrasia of Acne Vulgaris in Women, Endocrinology **27**:755 (Nov.) 1940.

2. Grollman, A.: Essentials of Endocrinology, ed. 2, Philadelphia, J. B. Lippincott Company, p. 570.

to warrant some conclusion as to the therapeutic value of administration of the hormone. All patients, with the possible exception of 1, seemed to benefit. The dose, which in most cases can be rather small, must be adjusted to the individual. My impression is that combination of the natural with the synthetic estrogens is best, although the synthetic estrogen alone frequently works. As a control with male subjects testosterone proved unsatisfactory, but the use of vitamin A for the same purpose was satisfactory. At no time was there evidence that this vitamin had any real therapeutic value in the male as contrasted with the effect of the estrogens in the female. As yet no opinion can be rendered as to the permanency of the effect of estrogens administered artificially, although in this study the results apparently were permanent. Probably the best criterion of my deductions from this study is the fact that I now practically promise the female patient with acne a satisfactory result whereas my results in treatment of acne of male patients are about the same as they always were.

## ABSTRACT OF DISCUSSION

DR. STUART C. WAY, San Francisco: The use of hormones in the treatment of acne is not new although to date it has been more or less empiric. It seems strange that the commonest cutaneous disease, acne, should be characterized by such a diversity of opinions from the standpoint of therapy. In acne as in many other dermatoses, our weakness lies in that we attempt to treat symptomatically rather than etiologically. The onset of acne rarely prior to, or as a rule during, adolescence (and in some instances, its persistence throughout the period of normal sex activity) can imply that sex hormones are important causative factors. My experimental studies to date have yielded results that are in accordance with those of Lawrence and Werthessen who in 1942 proposed the thesis that acne is caused by a disturbance of the normal balance between androgens and estrogens.

Dr. Goeckerman has given us a paper on a subject which, judging from the literature, I am sorry to say has been of more interest to the endocrinologist than to the dermatologist. On the other hand, there are a few diseases of the skin that are more worthy of study than acne. Then, some persons, including Urbach, have claimed that the aggravation of acne during the premenstrual phase was due to the presence in the blood of an endogenous allergen. Zondek likewise expressed the opinion that acne could be partially explained on an allergic basis because he was able to demonstrate a dermal sensitivity in certain patients suffering from acne. Studies to date have shown decided fluctuations in the daily urinary excretion of androgens and estrogens in normal men and women. However, there is no definite evidence of a monthly cycle in the excretion of either androgens or estrogens in normal men, while in normal women the excretion of estrogens is characteristically low during the menstrual period and normally rises to higher levels during the intermenstruum. If or when acne is caused by androgen or estrogen unbalance, it seems reasonable to assume that such an unbalance may be due in certain persons to a deficiency and in others to an excess. It is also logical to assume that such a deficiency or excess may be estrogenic in one instance and androgenic in another and that it is subject to variation in the same person. These comments are based on personal observations carried out during the past three years. While I am firmly convinced of the value of hormones in

treatment of both male and female patients, I feel that other causative factors exist for 57 per cent of all (female) patients with acne and that they should be carefully evaluated before instigation of therapy.

DR. U. J. WILE, Ann Arbor, Mich.: I am particularly interested in the results which Dr. Goeckerman has brought out in the treatment of acne with estrogenic substance. Many of the members of the Association may remember "Studies on the Sex Hormone in Acne" (ARCH. DERMAT. & SYPH. **39**:200 [Feb.] 1939), which I presented at our Sixty-First Meeting at Del Monte, Calif., in 1938. The results, based on a long series of studies on acne in both men and women, tended to show that both men and women suffering from acne have a decidedly lower estrogenic output than do normal persons in the same age group. The low estrogenic output in men explains adequately Dr. Goeckerman's failure to influence acne in men by treating them with androgen. Obviously this would further disturb the abnormal ratio between androgen and estrogen which exists in both sexes.

Indication from the experimental side that the adolescent type of acne is a sex hormone imbalance was further shown in our contribution by the fact that the ratio between an androgenic and estrogenic output was quite different in patients with acne in both sexes than in normal persons of both sexes. In our experiments my associates and I determined estrogenic output according to the extraction method of Frank and Goldberger, using the rat unit for bioassay.

In this method extractions of estrogen in twenty-four hour urine were injected into castrated rats to produce estrus. In our studies of androgen in both sexes, with and without acne, the extracted androgenic substance was injected into capons and the androgenic percentages were rated in capon units.

From these results it appeared to us that treatment based on reestablishing the normal ratio between estrogen and androgen was a logical procedure in connection with local treatment for the therapy of acne.

The spontaneous cure of acne following the completion of adolescence and the entrance into the marital status would seem to indicate the restoration of the normal ratio between estrogen and androgen.

DR. F. J. EICHENLAUB, Washington, D. C.: Up to now my experience with the use of estrogen has been disappointing.

Since acne occurs after the age of thymus degeneration, it seemed possible that this gland might be the balancing agent in that part of the endocrine system controlling the sebaceous glands.

An extract of thymus gland for injection was secured, and up to 5 cc. was administered twice weekly intramuscularly. There was improvement in some cases, but no striking results.

So far as I can determine, this was the first attempt to use thymus extract as an injection in human subjects.

DR. JOHN C. BELISARIO, Sydney, Australia: I was very much pleased to hear this paper because the subject is one in which I have been particularly interested in the last three years. There are many who believe that acne is partially or wholly due to a preponderance of androgenic over estrogenic hormones. Treatment along these lines has proved very helpful. Barbor, Bishop and Ingraham have been using this method of treatment for a considerable time. I have been using it for three years. The dose I have been employing is 0.5 mg. of diethylstilbestrol administered by mouth night and morning for eight to ten weeks in male patients. I have found that diethylstilbestrol is just as helpful for males as for females. With female patients I have given the same dose for ten days following the men-

strual period, up to three or four months. I have given it for longer times, but doing so tends to increase the likelihood of symptoms. In my experience, if the drug is given close to the commencement of a period, symptoms are more likely to occur. The symptoms which sometimes arise are taken as an indication to stop giving the drug. In male patients there may be soreness of the breasts. When administration is stopped no further complications occur. In female patients the symptoms may be interference with menstruation and morning nausea. I also use local treatment. I have given diethylstilbestrol routinely to all my patients except girls under 16. The fact that interested me was that prior to the advent of the estrogenic substances I could not obtain more than 5 per cent of cures without the additional use of roentgen irradiation. I have now increased the cures to about 25 per cent without the use of roentgen irradiation. I think that is a worth while increase. A number of dermatologists in Sydney now employ androgen therapy. It by no means leads to a certain cure, but it is a very useful adjunct to other methods of treatment. Another interesting adjunct that I have tried and which is recommended by Urbach is the intracutaneous injection into female patients of serum of blood withdrawn during or just before the menstrual period. After a few injections at two to three day intervals, one may often see improvement. I have also used other methods, such as the administration of large doses of vitamin A by mouth, nicotinamide and pyridosine. The combination increases the percentage of cures. I wish to thank Dr. Goeckerman for his paper, which I appreciated hearing.

DR. SAMUEL AYRES JR., Los Angeles: This subject has been of considerable interest over a long period of time, but there is one phase which I have not heard discussed, namely, the incidence of acne in those persons who have not matured sexually. The only case I have observed was of a young woman in her early twenties who had menstruated once. She was given estrogenic hormone, and about three weeks later acne developed for the first time.

DR. M. T. VAN STUDDIFORD, New Orleans: There is one phase of acne that was not discussed, and that is the phase after pregnancy. In a paper I read years ago I noted that ovarian extract was very effective in treatment of post-pregnancy acne, and I also noted that those who looked like the parent of the opposite sex would have a more persistent acne than would those who looked like the parent of the same sex.

Dr. Van Studdiford: To what paper do you refer? Please give bibliographic information.

DR. WILLIAM H. GOECKERMAN, Los Angeles: I appreciate the discussion. I should like to emphasize that I was very surprised when I first became aware that I was doing something worth while with estrogen. I had no particular scheme in mind; use of the hormone was simply an office procedure. As I continued, I became increasingly impressed with its value. I stated in the paper that I looked on this study as clinical investigation, and I therefore limited its observation to the use of estrogen in acne of the female. The point of the paper was that in my opinion the use of estrogens in female patients with acne is valuable. The discussions brought out some interesting points, and probably all merit further study. With reference to Dr. Belisario's point, the obtaining of benefit in acne of male patients by the administration of estrogens, I can only say that in a few cases in which I tried it, those of the cystic type found in men who had returned from the South Seas, it was more than useless. Dr. Wile has long been known to have carried out critical scientific studies on the hormones found in acne. My work was clinical.

# PERSISTENT, ABERRANT MONGOLIAN SPOTS

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AND
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THIS paper is devoted to the subject of persistent, aberrant mongolian spots, and a few comments will be made on differentiation of this condition from extensive blue nevus. Four cases are reported.

## REPORT OF CASES

CASE 1.—Interest in the subject was first aroused through observation of a 23 year old Negro woman who presented a pigmented area on the left side of her face and nose, and bluish spots in her left eye, which spots had been present since birth. There was a palm-sized macular area of grayish green pigmentation on the left side of her face, extending from in front of the ear to the angle of the mouth, with a smaller spot on the side of the nose. In addition there were four discrete bluish macules on the left sclera.

Histologic examination revealed a normal epidermis and dermis except for hemosiderin-free, dopa-positive melanoblasts situated in the middle third of the corium. The coarse pigment granules were contained in stellate and spindle-shaped cells which were quite dispersed and not sharply circumscribed in clumps. The upper portion of the corium was free of pigment and nevus cells. (Slides were later submitted to Dr. Hamilton Montgomery, who concurred in the diagnosis.)

This patient was presented before the Cleveland Dermatological Society as having an aberrant, persistent, mongolian spot.[1]

CASE 2.—Through the courtesy of Dr. Hamilton Montgomery and by consent of the authors, we are able to incorporate in this report material in connection with the case of Jensen and Haffly.[2]

Under the title, "An Unusual Case of Progressive Melanosis Oculi," Jensen and Haffly described the case of a 40 year old Chinese with a pigmentary disorder involving the right eye, the right side of the face, the forehead and the scalp. According to the patient, his parents had first noted a small pigmented

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Read before the Section on Dermatology and Syphilology at the Ninety-Eighth Annual Session of the American Medical Association, Atlantic City, N. J., June 9, 1949.

From the Department of Dermatology and Syphilology and the Institute of Pathology of Western Reserve University School of Medicine and of the University Hospitals.

1. Hubler, W. R.: Blue Nevus, or Mongolian Spot, Arch. Dermat. & Syph. **50**:417 (Dec.) 1944.

2. Jensen, C. D. F., and Haffly, G. N.: An Unusual Case of Progressive Melanosis Oculi, Am. J. Ophth. **31**:1476, 1948.

Fig. 1.—Extensive grayish green spots on the cheek and the sclera in a Negro woman aged 23 (case 1).

Fig. 2 (case 2).—Persistent mongolian spots of the right side of the face and the conjunctiva bulbi (courtesy of American Journal of Ophthalmology and Drs. Jensen and Haffly, Seattle).

area on the right eyeball when he was 5 years of age. During the first two decades the lesion gradually increased in size but remained confined to the globe. In the second two decades, the pigmentation spread extensively over the right side of the face, nose, forehead and scalp.

As the authors put it, "There was a diffuse slate-gray, non-elevated pigmentation irregularly spread over the right side of his face, extending through the floor of the nose into the mucous membrane of the mouth. In the mouth the pigmentation was confined to the hard palate. The overall pigment picture might be likened to the end result of a severe powder-blast burn." The conjunctiva, sclera, cornea and iris of the right eye and the iris of the left eye were similarly involved.

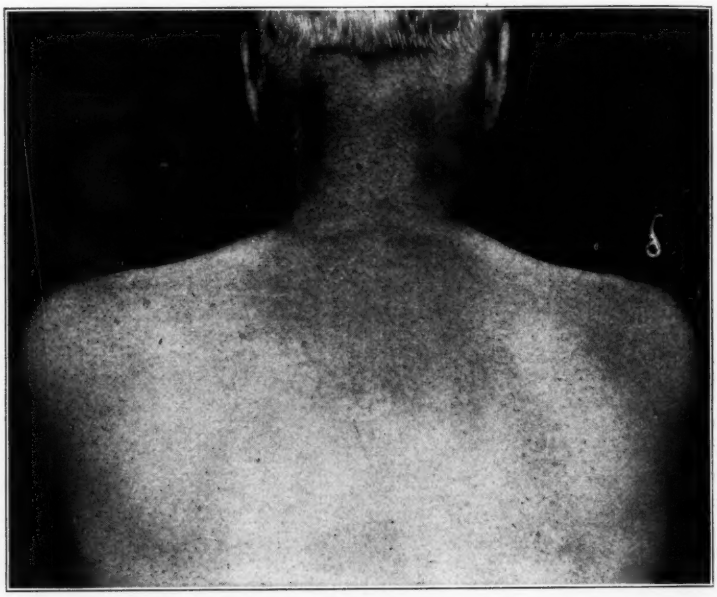

Fig. 3 (case 3).—Sixty-three year old white man with mongolian spot on the upper part of the back and the neck.

In the histologic sections, throughout the corium were numerous cells varying from stellate to fusiform in shape, filled with brown pigment. The cells were dispersed and not densely clumped, as might be expected in a blue nevus. There were no nevus cells. Unfortunately, no studies on the dopa reaction were made at the time, and it is not possible to make the test at present.

Case 3.—Also through the courtesy of Dr. Montgomery, the material from another case, originally seen by Drs. Montgomery and Brunsting at the Mayo Clinic, has been made available to us.

The patient was a 61 year old white man who presented an irregular, flat, slate gray plaque, measuring 17 cm. in diameter, over the upper portion of the back and neck. The lesion had been present since early childhood. In the report of the microscopic examination, Montgomery stated, "The histologic picture is

that of a mongolian spot plus senile skin changes. Pigment bearing cells in the cutis are spaced much farther apart than one sees in the ordinary blue nevus." The dopa reaction was positive.

CASE 4.—The final case is that of a 25 year old, blonde white woman. The patient stated that, according to her parents, a bluish discoloration was noted on the eyes at birth. This same process was first observed on the eyelids in very early childhood, and while there was some progression and increase in intensity

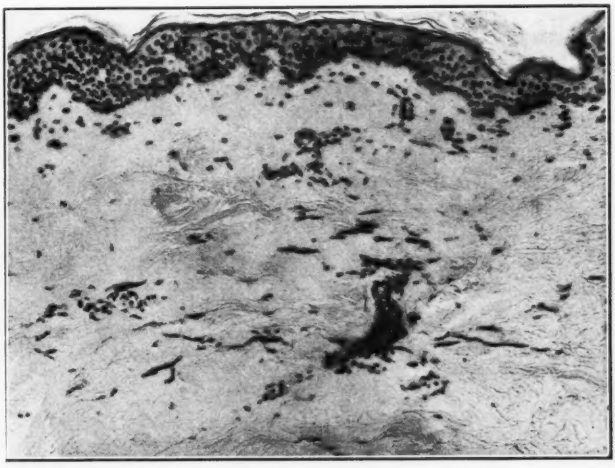

Fig. 4 (case 3).—Section of skin stained with hematoxylin and eosin; × 195. Note the widely spread melanoblasts with processes in the midcutis. The dopa reaction was positive.

Fig. 5 (case 4).—Note the macular grayish blue pigmentation of the lids, with the condition less evident on the forehead, and, likewise, the discrete bluish spots of the bulbar conjunctivas of both eyes.

during the first decade, the condition remained localized in the eyes and on the lids until early adolescence. During the second decade, there was extension of the condition onto the forehead and temples. It was felt by the patient that since the twenty-first year there had been deffinite regression. We had, at the time of writing, been following this patient for over a year, and it was our impression, also, that the intensity of pigmentation was fading.

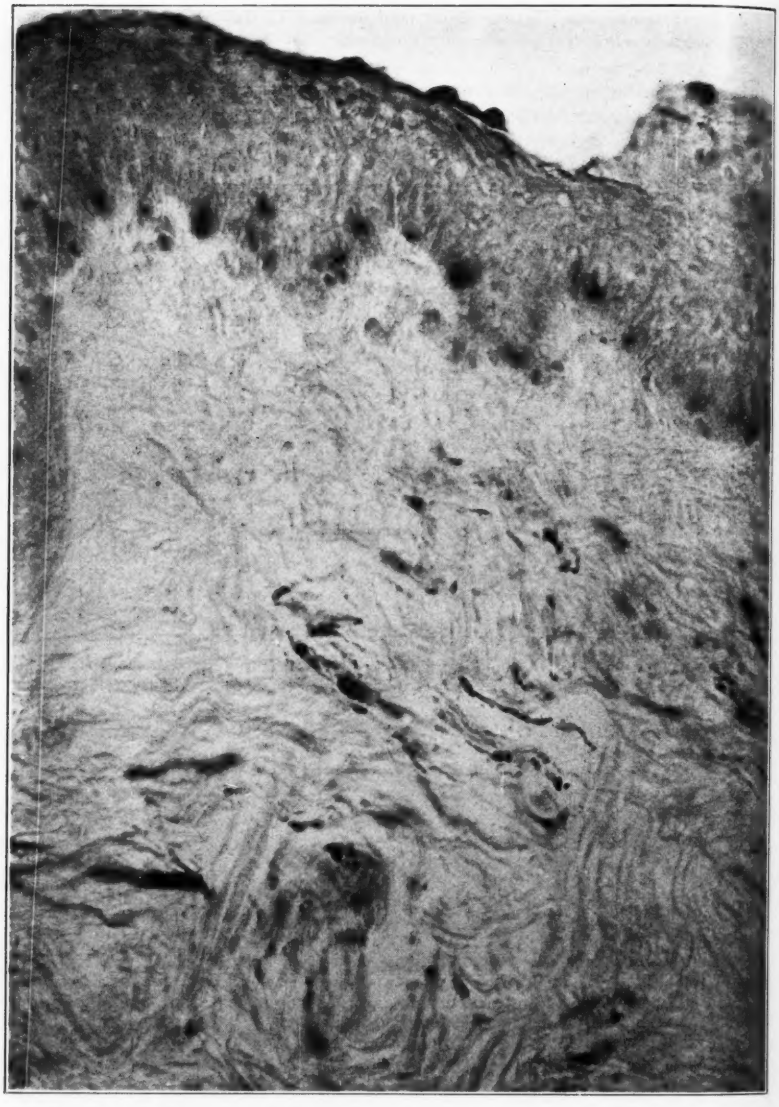

Fig. 6 (case 4).—The dopa reaction of the skin of the forehead was weakly positive; × 354. Note the scattered, fusiform cells with processes in the midcorium.

The family history was not significant. There were twelve siblings: seven brothers and five sisters. The patient was of pure Anglo-Saxon and Irish stock. No other members of the family were similarly affected. There was no evidence on physical examination, or from the history, of consanguinity, neurofibromatosis (von Recklinghausen's disease) or other pigmentary disorders.

Clinical examination revealed numerous discrete bluish spots on the bulbar conjunctivas of both eyes. The lids of both eyes showed a deep, macular, diffuse grayish blue discoloration, and as the process extended upward onto the forehead and temples, it became less and less evident. The almost perfect symmetry was an additional striking feature. At the periphery of the lesion, the pigmentation appeared to fade away gradually and blend into the color of the normal surrounding skin.

The patient insisted that the specimen for biopsy be removed from a very light blue area next to the hair border. Permission for the taking of further specimens was denied.

The sole feature presented by the microscopic section was the pigmentary abnormality confined to the dermis. There were numerous, scattered fusiform cells containing pigment granules which gave the histochemical reaction for melanin as demonstrated by silver impregnation. These cells were most pronounced in the midcutis and lower portion of the corium. The dopa reaction was weakly positive.

## HISTORICAL REPORTS

Meirowsky [3] stated that the Danish missionary Soabye in 1778 reported that the children of Greenland were born even as white as the Europeans but that they laid a 10 shilling piece–sized bluish mark over their sacral area which gradually spread over the entire body and was, perhaps, the cause of their dark complexion. Another Danish missionary, Hans Fabie [4] in 1816 mentioned the presence of a bluish birthmark on the sacrum of the children of Greenlanders, and Eschricht [4] in 1849 described an analogous process in Eskimos. Riedel,[3] as early as 1847, noted the so-called mongolian spots on babies in the Celebes and wrote about them to Charles Darwin. Darwin expressed the belief that the spots were an atavistic indication that the forebears of the patient had had a tinted back side.

## NAMES FOR MONGOLIAN SPOTS

In 1905 an American physician, A. S. Ashmead,[5] for a long time head of a large hospital in Japan, wrote of the spot as "the mulberry colored spot." He stated that it was called in various localities as fol-

3. Meirowsky, E.: Idiotypische Pigmentanomalien, in Jadassohn, J.: Handbuch der Haut- und Geschlechtskrankheiten, Berlin, Julius Springer, 1933, vol. 4, pt. 2, pp. 588-795.

4. El Bahrawy, A. A.: Ueber den Mongolenfleck bei Europäern, Arch. f. Dermat. u. Syph. **141**:171, 1922.

5. Ashmead, A. S.: The Mulberry-Colored Spots on the Skin of the Lower Spine of Japanese and Other Dark Races: A Sign of Negro Descent, J. Cutan. Dis. **23**:203, 1905.

lows: Samoa, *ole-ila;* Hawaii, *he-ila;* Central America, *nits gran;* Negroid sections of Brazil, *geni papo;* coastal province of Argentina, *mancha morata,* and Germany, *Mongolen-fleck.* In France it is variously designated as *tache bleue, tache mongolique, tache pigmentaire* and *tache bleue sacrée.*

### INCIDENCE OF THE LESION

As would be expected, the incidence of this spot varies with different races and parts of the world.

El Bahrawy [4] asserted that the spot or spots will be found in 90 to 100 per cent of Mongolians, 100 per cent of Malayans, 85 per cent of Bolivian Indians, 65 per cent of Negroes in Brazil, 52 per cent of mixed races in Brazil, 2 to 5 per cent of Italians in Brazil, and 1.5 per cent of white persons in Brazil. One per cent of white persons in Paris will have the spot, and 7.5 per cent in Montevideo, he stated. Von Bulow, quoted by Meirowsky,[5] said that on persons born from the union of white persons and Samoans the spot is not so frequent but that on those from the union of halfbreed Samoans and Samoans they are very common.

Fischer and Shen Chen Yü [6] estimated that 90 per cent of Polynesians have mongolian spots and 90 to 99 per cent of Japanese. They expressed the opinion that 98 per cent of the newborn in China have the spot, and 90 per cent of the newborn in Japan.

Chemin [7] studied the frequency of occurrence of the spots in China and found them in 89 per cent of children 0 to 1 year old, 71 per cent of children 1 to 3 years old and 19 per cent of children 3 to 8 years old.

Adachi [8] stressed the point that it is only a difference in percentage between the incidences in Mongolian and in European stock. As El Bahrawy well put it, "The mongolian spot is no exclusive index of the Mongolian races, but rather a well spread manifestation of the entire human race."

### APPEARANCE, DISAPPEARANCE AND PERSISTENCY OF THE LESIONS

The mongolian spot is generally present at birth or shortly thereafter, rarely later. In a large proportion of cases it will gradually fade out over a period of a few years; witness the previously cited figures

6. Fischer, W., and Shen Chen Yü: Kurzer Beitrag zur Kenntnis des Mongolenfleckes, Arch. f. Schiffs- u. Tropen-Hyg. **23**:447, 1919; Einiges über den Mongolenfleck, ibid. **23**:450, 1919.

7. Chemin: Taches congenitales de la region sacro-lombaire, Rev. de l'École d'anthrop. de Paris **9**:196, 1889.

8. Adachi, B.: Mongolen Kinderfleck bei Europäern, Ztschr. f. Morphol. u. Anthrop. **6**:132, 1903; Hautpigment beim Menschen und beim Affen, ibid. **6**:1, 1903; Anat. Anz. **21**:16, 1902.

of Chemin's findings in China. Katô [9] made the assertion that the pigmentation gradually fades up to 4 years and thereafter more rapidly, until by the thirteenth year it is seldom seen.

Fischer and Shen Chen Yü,[6] working in Shanghai, found it in 57 of 63 patients under 4 years of age, in 23 of 47 patients over 4 years and under 7 years of age, in 3 of 15 patients over 7 years and once in a 14 year old child. The spot, they stated, rarely lasts the entire life. Nevertheless, it may occur even if it does not show grossly. Ishikawa, [10] in histologic studies of the bodies of Japanese from the ages of 18 to 82, found typical "mongolian cells" in all of them although the cells were less frequently encountered in examination of older persons. Moreover, study of the fetus revealed the gross appearance of the spot by the fifth to sixth month, and Ishikawa found the pigment cells in the beginning of the third fetal month in very sparse numbers. From the fifth month on, they were present almost without exception.

## SITE OF THE LESIONS

The typical site of the lesion is well known to all—the region of the lumbosacral junction and perhaps the contiguous inner aspect of the buttocks. In a fair proportion of the cases that area is the only site. El Bahrawy said that far less frequently the lesion is found on other parts of the body—breasts, abdomen, extremities and face. It may be present at birth or appear somewhat later. In adult Japanese it is seldom found and then in relatively unusual locations. El Bahrawy quoted Balz to the effect that, rather than the spots being a typical identification mark of the Oriental, analogous spots may be found in all races and peoples, although in different incidences and intensities.

Wateff [11] studied the frequency of occurrence of the lesion in Bulgaria and said that, in addition to the areas stated, it will be found rarely on the back and very rarely in other areas. Fischer said that spots on the ventral surfaces are much rarer. He stated that Cozzolino saw a male child with the typical sacral involvement and another spot on the lower part of the thigh, whose brother had a 7.5 by 5.5 cm. spot on the left side of the anterior portion of the pelvis. Wateff thought there was more tendency to involvement of the left side of the body among the 3,500 infants (Bulgarian, Macedonian, Jewish and Bohemian) that he studied and among whom he found 20 bearers of one or

9. Katô, T.: Anatomo-histologische Studien über die sogen. Kinderflecke, Mitt. a. d. med. Fakult. d. k.-jap. Univ. zu Tokyo **6**:377, 1905.

10. Ishikawa, N.: Ueber den sogenannten Mongolenfleck bei japanischen Föten, Folia Anat. Japon. **2**:1, 1924.

11. Wateff, S.: Taches pigmentaires chez les enfants bulgares, Bull. et mém. Soc. d'anthrop. de Paris **8**:231, 1907.

more spots. All had the sacral involvement. Several had bizarre, diffusely pigmented areas of the trunk—in 6 of them, over almost the entire back. One had a spot on the dimple of the upper lip and another lesion on the chin, while 1 patient had two spots on the vertex of the head.

In Ebert's case,[12] of a Mexican child aged 2½ months, there were bluish black macules on the buttocks and sacrum, several coin-sized bluish spots over the back, a large spot on each shoulder and a lesion on the left knee.

In discussion of Ebert's case, Drs. Edward Oliver Sr. and Clark Finnerud stated that they had observed a patient a year earlier with spots on the leg, several on the body, a well demarcated one above the ankle and one on the thigh. Eleven months later these spots were much paler. Dr. Finnerud stated that he had also seen an Indian infant with almost half of the body, including the face, neck, ears and lower extremities, involved.

Adachi observed spots situated in front and in back of the ears. Sekiba [13] observed the mongolian spot on the face twice in adults, and said that a colleague, Tashiro, had a child of his own with many extensive spots on the buttocks and extremities, and that the father removed one from the forehead surgically. Königstein, according to Wateff,[11] observed the condition on the back of the hand and on the neck.

Strangely enough, involvement of the region of the eye is not unheard of. Adachi,[8] in his extensive study, pointed out that in anthropoid apes there is a strongly pigmented skin of the eyelids even in those that have a relatively pigment-free skin on most parts of the body. The conjunctivas of apes, he stated, is not pigment free.

Reese,[14] a well known American ophthalmologist much interested in the problem, made the assertion, "The extrasacral spot and the blue nevus are seen principally on the face and extremities, and may appear on the lids and bulbar conjunctiva."

Another well known American physician, William Allen Pusey,[15] as long ago as 1916 reported the case of a Chinese university student with a flat, brown to black nevus, not hairy, of the right side of the face. There was, in addition, a spot of bluish pigment on the sclera.

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12. Ebert, M.: Mongolian Spots, Arch. Dermat. & Syph. **17**:256 (Feb.) 1928.

13. Sekiba: On the Bluish Black Spots, J. Anthropol. Soc. Tokio **3**:22, 68, 1887.

14. Reese, A. B.: Pigmented Tumors (The DeSchweinitz Lecture), Am. J. Ophth. **30**:537, 1947.

15. Pusey, W. A.: Facial Pigmentation Involving the Sclera, Ophth. Rec. **26**: 18, 1916.

Leber and Prowazek [16] stated that there is occasionally a pigmentation of the scleras in the natives of Samoa and that it gradually fades with age.

Fischer and Shen Chen Yü observed the spot on the bulbar conjunctiva three times and have seen spots on the body the size of the flat of the hand.

### COLOR OF THE MONGOLIAN SPOT

The color of the mongolian spot has been variously described as light blue, blue, grayish blue, dark blue and mulberry. It has been compared to that of the tattooage observed from gunpowder. Occasionally it may be a slate gray tint. At times there may be a main island with lighter spots around it. In Negroes the lesion may even be grayish green, as observed in our case 1, and ordinarily the tint is darker in a person with a dark complexion. In Eurasians the color is lighter and generally disappears earlier.

### SIZE AND SHAPE OF THE LESIONS

The lesion may be irregularly round, roughly triangular, ovoid, heart shaped, angular or formed like a horseshoe, lance or tennis racquet. Only very exceptionally there may be hairs. Meirowsky [3] and other authors emphasized the absence of hair. The area may vary in size from 0.5 to 5.0 cm. in diameter, and Bruch [17] said that the spot may extend over a very large area. Fischer and Shen Chen Yü [6] stated that the size ranged "from that of a bean to the flat of the hand." The entire half of the back may be included. Zebra-like configurations may be found.

### MICROSCOPIC OBSERVATIONS

The characteristic picture in this condition is the finding of the so-called "Mongolian cell."

El Bahrawy,[4] an authority on the subject who studied at Bloch's clinic, described the cells as long, spindle shaped, irregularly wavy, 5 to 10 microns thick and 30 to 50 or 100 microns in length. The center is the widest portion with a pale, oval, lightly staining nucleus that shows up in an unstained specimen as a light spot. The cells may have long processes and may be bipolar or irregular. Some cells are flat, others pear shaped.

Grimm [18] said that the processes of the cells may be serpentine or straight, stretching out into the connective tissue, even seemingly to

16. Leber, A., and von Prowazek, S.: Bericht über medizinische Beobachtungen auf Savaii und Manono (Samoa), Arch. f. Schiffs- u. Tropen- Hyg. **15**:409, 1911.

17. Bruch, A.: Notes sur la tache bleue sacrée dite mongolique, Arch. de méd. d. enf. **15**:446, 1912.

18. Grimm, F.: Beiträge zum Studium des Pigments, Dermat. Ztschr. **2**:328, 1894-1895.

anastomose with neighboring cells. In children of the white race, the pigment granules may be so few that the cells are difficult to differentiate, especially in older children.

Adachi,[8] a Japanese authority on the condition, stated that the cells are found deep in the corium of the pigmented areas. Katô [9] said that in the first week of life they may be found even in the upper part of the corium as well—later, only in the lower portion. They are arranged between the connective tissue fibers and usually lie parallel to the epidermis. Some may be found around the vessels.

In fresh unstained material from 10 cases in the newborn at Shanghai, Fischer [6] described the pigment as light yellow or brown, or a much darker, yellowish brown, brown-black or black. The pigment in fine kernels fills the entire cell.

Adachi stated that in apes, while there is some variation, the cell is found almost uniformly in the deep part of the corium. He pointed out that there are two kinds of pigment cells in the corium of man and apes: one small and in the upper layers, and another, deeper, the deeply placed cell being the mongolian cell. All the authors stress the location of the cells in the lower third of the corium.

> They begin to appear in the foetus as early as the third month, and from the fifth month on they are present almost without exception. . . . Moreover, even after the disappearance of the spot anatomically, microscopic study in corpses may reveal their presence from thirteen to eighty-two years.[10]

Masson [19] and Becker [20] differentiated the pigment cells in the upper part of the corium as melanophores (carriers of pigment), the more deeply situated cells being classified as pigment-producing melanoblasts. The latter are "dopa positive." Masson appeared to look on these cells in a way as glandular cells; i. e., producers of pigment. However, he stated, "Stress must be put on the fact that a melanoblast may lose, at the same time, its dopa reaction and its aptness to produce pigment." It is our feeling that 1 patient whose case is reported here (case 4) is probably in this stage. Moreover, she apparently is losing some of the intensity of her pigmentation. Bloch [21] himself presented 2 babies illustrating this point before the Swiss Dermatological Congress at Zurich in July, 1920. The slate-colored spots on the sacrum of each showed cells with melanin, black on contact with silver nitrate and osmic acid and light on

19. Masson, P.: Pigment Cells in Man: The Biology of Melanomas, New York Acad. Sc. **4**:15, 1948.

20. Becker, S. W.: The Biology of Melanomas, New York Acad. Sc. **4**:82, 1928.

21. Bloch, B.: Zwei Fälle von Mongolenfleck bei Säuglingen, Schweiz. med. Wchnschr. **51**:116, 1921.

contact with hydrogen peroxide. For both the dopa test was negative. Masson [19] would put it thus in such a case: "The melanoblast persists as a cell and deserves to retain its name, but it may be considered as inactive."

Montgomery and Kahler [22] said that the melanoblasts in the blue nevus are denser and may be grouped in irregular masses in the lower two thirds of the cutis, but that they may even be found high up under the epidermis. They are thickest in the center and give a positive dopa reaction, and disturb the normal arrangement of the connective and elastic tissue. Moreover, the blue nevus is usually raised slightly above the surface. It may be localized or rarely diffuse. Thus, Upshaw, Ghormley and Montgomery [23] reported the case of a white boy, aged 9, with an extensive blue nevus on the left flank, 17 cm. long and 3 to 6 cm. wide. Microscopic study showed the cells of the growth to be dermal melanoblasts, while nevus cells, pigmented in type, were not present. The melanoblasts had long, bipolar, dendritic processes and the dopa test was positive. The dense masses of cells as seen in the lower dermis are never seen in the mongolian spot. Moreover, judging from clinical experience and a study of the literature, we are not aware that any true mongolian spot shows the "multiple, fine, dark blue, round nodules, slightly raised above the skin and with the bluish discoloration in the intervening small areas between the circumscribed nodules." These two items clearly differentiate the mongolian spot and the rare extensive blue nevus.

## COMMENT

In this connection, Carleton [24] very recently presented a remarkable case of bluish, bruiselike spots of pigmentation in a white girl aged 14. It appeared first at birth on the sclera and iris of the left eye, and later, at the age of 3, on the back, behind the ears, margin of the forehead, nose, lips and vestibule of the mouth. Some of the spots kept forming up to the age of 9 years, and once formed they did not alter their appearance. The girl also had a bossy thickening of the skull behind the ears, although there was no evidence of increased intracranial pressure or cerebellar dysfunction. Carleton very expressively described the color of the sclera as similar to the stain from "spilt ink." Microscopic examination of the skin revealed a widespread infiltration of dendritic bipolar cells containing fine brown pigment granules giving the histochemical reaction of

22. Montgomery, H., and Kahler, J. E.: The Blue Naevus (Jadassohn-Tieche): Its Distinction from Ordinary Moles and Malignant Melanomas, Am. J. Cancer **36**:538, 1939.

23. Upshaw, B. Y.; Ghormley, R. K., and Montgomery, H.: Extensive Blue Nevus of Jadassohn-Tieche, Surgery **22**:761, 1947.

24. Carleton, A.: Diffuse Mesodermal Pigmentation with Congenital Cranial Abnormality, Brit. J. Dermat. **60**:10, 1948.

melanin. The cells were around the blood vessels and sweat ducts, and scattered through the dermis, particularly the deeper portion. One specimen gave a positive, another a negative, reaction to the dopa test.

In discussion, Parkes Weber expressed the opinion that the condition was a "forme fruste" of neurofibromatosis, showing pigmentation only, and he stated that in 1 of his cases the color was likewise blue. The point was raised by Carleton that neurofibromatosis is a justifiable diagnosis only in the event of a strong familial history. In her case there was no such history. There was no consanguinity, and the patient was of pure British stock and the only one affected in a family of three.

Carleton stated that she did not think this condition could be a blue nevus, which is localized, nor a mongolian spot, which is rare in Europeans. In the latter, the lesions are present at birth and gradually disappear. She expressed the opinion that in the distribution and in the appearance of spots on the sclera at birth, becoming more conspicuous up to the age of 9, the disorder differed considerably from mongolian spots.

Carleton stated that she wondered about its possible relation to a diffuse melanosis described by Hadwen [25] in cattle and horses, especially Percherons, which grow gray and white with age. In these, melanin-containing cells are found around sweat glands and blood vessels and also in the periosteum, lymph nodes and muscles. The deposits begin early, at 6 years or more, and gradually increase.

Carleton expressed the opinion that her case represented a diffuse abnormality in mesodermal pigmentation not exactly comparable with any hitherto described condition and associated with an unusual cranial abnormality.

Except for the osseous changes in the skull in Carleton's case, there is much similarity between her case and our case 4. In neither was there a familial history of neurofibromatosis nor of any pigmentary disorder. The involvement of the vestibule of the mouth in Carleton's case and in the case of Jensen and Haffly are likewise quite similar, and as far as we can find they are the only cases in the literature showing this form of involvement. As has been mentioned, different authors emphasize that in aberrant types of mongolian spot and of blue nevus the face and conjunctivas are prone to be involved.

## CONCLUSIONS

While the mongolian spot is seen most frequently over the sacral area, it is also encountered on other parts of the body. Reese made the statement, "The extrasacral spot and the blue nevus are seen principally on

25. Hadwen, S.: The Melanomata of Grey and White Horses, Canad. M. A. J. **25**:519, 1931.

the face and extremities and may appear on the lids and bulbar conjunctivae."

The number, size and shape of the spots vary greatly.

The color varies all the way from a light blue in a blonde to a grayish green in the Negro.

It is found most frequently in the Mongolian and Negroid types, but may be encountered in white persons as well, though such an occurrence is relatively rare.

Rarely the mongolian spot or spots may appear after birth and continue to spread for a period of years.

Microscopically the so-called mongolian cell, found in the lower part of the cutis, is a long fusiform cell, 5 to 10 microns wide and 25 to 75 microns long, often having several dendritic processes. The pigment in an unstained specimen is found throughout the cell as very fine granules, light brown to a darker yellowish brown. The pigment is melanin with a positive dopa reaction. Rarely, in a receding spot, may the dopa reaction be negative. The cells are found between the connective and elastic tissue fibers and are parallel to the epidermis. They are not clumped together, causing distortion, as in a blue nevus.

The very rare extensive blue nevus clinically differs greatly from the mongolian spot. The color is not uniform, and the surface of the skin may be irregular.

A report is made of 4 cases of aberrant, persistent mongolian spot; one of the back and neck, and 3 showing extensive involvement of the eyelids, forehead and bulbar conjunctiva. In 1 instance there was also an area on the hard palate. This last case and the probable case of Carleton's are the only 2 cases thus far reported with mongolian spot of the oral surfaces.

ADDENDUM.—Through the courtesy of Dr. Hamilton Montgomery, we have had the opportunity of reviewing a study by Drs. Harry Pariser and Herman Beerman which has just appeared in print, entitled: "Extensive Blue Patchlike Pigmentation: A Morphologic Variant of Blue Nevus? Persistent Extrasacral Mongolian Blue Spot? Diffuse Mesodermal Pigmentation?" [26]

A white woman aged 34 first noticed a diffuse bluish pigmentation of the forehead at about 20 years of age. This later spread to the scleras of both eyes and to the cheeks. Histologic examination showed a band of melanin-positive, spindle-shaped cells in the midcutis. There was no disruption of the connective tissue or elastic tissue.

26. Pariser, H., and Beerman, H.: Extensive Blue Patchlike Pigmentation: A Morphologic Variant of Blue Nevus? Persistent Extrasacral Mongolian Blue Spot? Diffuse Mesodermal Pigmentation, Arch. Dermat. & Syph. **59**:396 (April) 1949.

While the histologic changes were more suggestive of mongolian spot, Drs. Pariser and Beerman expressed the opinion that this variant might better be termed blue nevus.

It is very difficult, if not impossible, to draw a sharp dividing line between mongolian spot and blue nevus, but for reasons cited in this paper we wonder whether it would not be preferable to attempt to more sharply define and distinguish the two conditions.

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## ABSTRACT OF DISCUSSION

DR. S. R. MERCER, Fort Wayne, Ind.: We are fortunate that the authors have been able to report 4 cases of such an unusual dermal and ocular melanosis. Clinically, the disorder is harmless, except from the cosmetic viewpoint. I have been able to find no record of melanoma originating in such a lesion. Etiologically the appearance of dermal melanosis, in the form of either mongolian spot or blue nevus, is usually thought to be atavistic. Some of the anthropoids normally exhibit dermal and ocular melanoblasts. That the incidence of sacral spots does not parallel the depth of epidermal pigmentation is apparent from the fact that these spots are seen in practically 100 per cent of Mongolians, who are not always deeply pigmented. MacFarlane (*Science* **95**:431, 1942) found sacral spots in 38 of 50 Bengalese infants. One nurse from the Himalayan region stated, "We call it the sign of a Hill baby," the Hill people being Mongoloid, Nepalese and Tibetan. Sacral spots were found by MacFarlane in all of 15 Javanese babies, but not in those of Dutch parentage or hybrids of Dutch and Javanese. Matus (*South African M. J.* **15**:121, 1941) found with regard to the South African Negro that the pigmented spot was present macroscopically in 75 per cent of the infants studied. His material was drawn from a study of a group of 50 female and 50 male babies, the exact number of spots being 35 in the male group and 40 in the female babies.

Brennemann (*Arch. Pediat.* **24**:426, 1907) estimated that the sacral spot occurs in at least 95 per cent of the Negro children in Chicago. It is evident that racial as well as hyperpigmentary factors are involved.

From the academic viewpoint concerning nomenclature, the use of the term "aberrant mongolian spot" may be questioned. One might insist that the term be used only to designate blue plaques seen in association with sacral spots. Such a sacral spot was not mentioned in any of the 4 cases. The true mongolian spot usually fades out during the first few years of life, while the aberrant spots may have their onset later in life and extend to cover larger areas.

Bettley (*Brit. J. Dermat.* **50**:181, 1938) expressed preference for the designation "progressive melanosis" and stated that, clinically and histologically, the plaque which had appeared at the age of 14 in his 30 year old patient resembled a blue nevus. He also suggested a resemblance to benign progressive melanosis as described by Hadwen in horses and cattle. To my mind the latter process is more extensive and deeper; it approaches malignancy. On the other hand, blue nevi are usually smaller than the large plaques described by the authors. The Japanese (Tanino, H.: *Jap. J. Dermat. & Urol.* **47**:51, 1940) called a large bluish plaque on the face, often associated with ocular melanosis, "nevus fusco-caeruleus."

It may possibly be that the acquired progressive blue plaques bear as close a relation to mongolian spots as acquired nevus pigmentosus bears to the prenatal variety.

DR. HERMAN BEERMAN, Philadelphia: The authors have presented in admirable fashion the subject of persistent, aberrant mongolian spots based on the pertinent literature and four representative cases. The last word has not been said as to the exact nosologic position these flat, extensive, blue-black spots occupy. My interest in this subject was occasioned by study of an example of extensive blue patchlike pigmentation in a white woman of 34 years, who was first seen by Dr. Harry Pariser of Norfolk, Va.[26] The patient had first noted pigmentation on the right side of the forehead at about the age of 20 years. The process gradually spread until in 1946 there was involvement of the left side of the forehead, both cheeks and the left forearm. Careful study revealed a histologic appearance similar to that in Dr. Cole's cases, with particular concentration of the pigment cells (so-called mongolian cells) in the midcutis and with some tendency for concentration around hair structures. Our case departs from the original clinical description of the blue nevus of Tièche in three ways. First, the lesion is a bluish nonindurated patch involving an extensive area of the forehead, scalp, face and sclera. Second, it did not appear at birth or during childhood. Third, there is an extension of the process with age in contrast to the original description that the lesions remain static. Objectively this bluish pigmentation resembles the clinical description of extrasacral mongolian spot more than blue nevus. It differs in its course from the usual evolution of extrasacral mongolian spot in that it increased in intensity with age and appeared for the first time in adult life.

Because of the strikingly similar histologic picture of blue nevus, mongolian spot and the variant found in my patient, I suggest that all these conditions be included in the concept of a single clinical entity. In order to avoid introduction of any new terminology, the name blue nevus seems most appropriate for this entity, particularly since the spot can occur in the non-Mongolian races and because this term mongolian spot fails to convey any indication of the nevoid origin or clinical appearance of the lesion.

DR. F. A. ELLIS, Baltimore: Dr. Cole has partly answered my question; I was interested in the problem of what happens to a mongolian spot as the patient gets older. It would be interesting to determine the percentage of melanotic babies that have the mongolian spots and at autopsy, the number of adults that still have the melanin-containing cells in the dermis in the buttocks. Why do the spots clinically disappear? I doubt that the melanin cells disappear, but I think that changes occur in the overlying structures so that pigment is no longer visible clinically.

DR. HAMILTON MONTGOMERY, Rochester, Minn.: The picture of the patient with extensive blue nevus which Dr. Cole showed is from a case reported by Drs. Upshaw, Ghormley and myself.[23] Histologically, the condition was a blue nevus with dense masses of dendritic cells in the corium. Fundamentally, there is no great difference between the cells of mongolian spot and those of blue nevus, but in the mongolian spot the cells are widely separated. The ordinary blue nevus usually occurs as a solitary lesion, or there may be a couple of lesions in the same patient. The blue nevus may occur anywhere on the body and has been mistaken for melanoepithelioma. It does not look like the aberrant or misplaced mongolian spot which Dr. Cole has presented. I, therefore, would prefer not to simplify the terminology and call everything a blue nevus. I agree that the term "mon-

golian spot" may be a misnomer, just as "sarcoid" is a misnomer. I think that these aberrant mongolian spots with cells widely separated, as they have been in the cases seen at the Mayo Clinic, in the cases of Jensen and in the cases of Cole and his associates should be separated from blue nevi.

Malignant change has not been reported in mongolian spot so far as I know. It has been reported in approximately 6 cases of blue nevus, 2 of which were reported by Darier and 1 by Stout in New York. In all the cases there was a history of preceding repeated irritation and trauma. Thus, we have the same story as in ordinary pigmented nevus, whether it is a junction nevus or hairy deep subepidermal mole developing into melanoepithelioma after repeated irritation and trauma. When a blue nevus undergoes malignant change, it is then a true melanosarcoma because the blue nevus cells are presumably of mesodermal and not of epidermal origin.

Dr. H. N. Cole, Jr., Cleveland: I should like to make the acknowledgment to Dr. Montgomery for the use of a photograph and photomicrograph of a 9 year old white boy whose case was reported by Drs. Upshaw, Ghormley and Montgomery. In reference to Dr. Ellis's question, it is difficult to say what becomes of the mongolian spot. Most commonly, the mongolian spot is present at birth and fades out rapidly over the period of a few years. Various workers have reported that at birth anywhere from 90 to 98 per cent of the members of the Mongolian, Chinese and Japanese races have these spots over the sacral region. Approximately 3 to 8 per cent retain these spots as late as the middle teens. In Jensen and Haffler's case, the patient had the condition confined to the eye and lid up to 20 years of age. It was only after that time that the pigmentation started to spread over the face onto the forehead and scalp. At the time of publication of their article the condition was still progressing.

The condition in our case, which seemed to be quiescent for a long period, apparently is now regressing. In other words, any number of possibilities may occur. I am not aware of malignancy having been reported in connection with mongolian spot. Whether these lesions should be termed mongolian spot of the extrasacral variety or extensive blue nevus is difficult to say. Of course, if there is dense clumping of the melanoblasts which causes distortion of connective tissue and if the lesion is raised above the skin, I think one is justified in calling the disorder an extensive blue nevus. However, in a case in which there is not such dense clumping of the dermal melanoblasts and in which the lesions are not raised, the category to which the case belongs is certainly open to question.

# PROTEIN DEFICIENCY IN CUTANEOUS DISEASE

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IN A PREVIOUS presentation,[1] the subject of nutritional eczema in the aged was discussed. In it my associates and I presented for consideration observations on patients past middle life who presented varying degrees of edema of the legs below the knees, associated with a chronic, erythematous, papular, vesicular, pustular, exudative or squamous inflammation of the skin involving the same areas. In these patients cardiac decompensation and renal disease were not found and varicose veins of sufficient degree of severity to cause the edma were not present. We suspected deficiency in serum proteins and found in many instances a decreased total serum protein with a reversal of the albumin-globulin ratio. This deficiency in aged persons was due to several factors: poor dentition with attendant low intake of meat, sketchy dietary habits of many elderly people, anorexia and impaired assimilation of proteins that were ingested.

I now wish to propose that such cutaneous changes can occur from protein deficiencies due to reasons other than those that operate in the aged, and, further, that protein deficiency can influence the course and prognosis of other cutaneous conditions.

## BRIEF REVIEW OF MODERN CONCEPTS OF PROTEIN METABOLISM

One of the prime processes in which body proteins are involved is the maintenance of balance in osmotic and hydrostatic pressure between the circulating blood and tissue fluids. The plasma proteins albumin, globulin and fibrinogen are the ones which maintain this balance. The so-called normal levels of these three plasma proteins are as follows: 7.1 Gm. of protein, with 0.27 Gm. of fibrinogen, 2.7 Gm. of globulin and 4.1 Gm. of albumin per hundred cubic centimeters. The approximate ratio of the three fractions is 1 : 10 : 15, with the albumin-globulin ratio being 1.51 : 1.00.

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Read before the Section on Dermatology and Syphilology at the Ninety-Eighth Annual Session of the American Medical Association, Atlantic City, N. J., June 8, 1949.

1. Guy, W. H.; Jacob, F. M., and Guy, W. B.: Geriatric Nutritional Eczema, Arch. Dermat. & Syph. **57**:822 (May) 1948.

Reduction in levels of these proteins in the circulating plasma is one of the main causes of clinical edema. Albumin, because of its greater concentration and the smaller size of its molecule, is the most important of the three in this osmotic effect. Formerly, the critical level of edema was considered to be 3 Gm. of albumin per hundred cubic centimeters of plasma. Below this level edema was said to occur.

The amount of protein in circulating plasma is not solely dependent on the amount of proteins ingested. The ingested proteins are first hydrolyzed into their constituent amino acids in the digestive tract and are absorbed into the portal circulation as such. A certain part of them are deaminized in the liver and converted into glucose, available for energy requirements. The rest are used for replacing tissue and plasma proteins, some of this replacement being done in tissues themselves and some of it being done by the liver. Albumin is thought to be produced by the liver, and globulin, probably in the reticuloendothelial system. The nitrogen derived from deaminized amino acids is excreted in the urine as nonprotein nitrogen. The output of the latter represents the sum of the nitrogen obtained from ingested protein used for energy requirements and the nitrogen from protein broken down in tissue catabolism. A person is considered to be in nitrogen balance when nitrogen excretion is equal to nitrogen intake over a period of several days.

At this point I wish to modify some of these classic concepts in light of recent investigations and publications. According to Stare and Davidson,[2] "The critical level of edema, normally considered as 3 Gm. of albumin per 100 cc. of plasma may be modified by certain situations such as anemia and edema may occur with levels greater than this." And Youmans [3] stated that "emphasis should be placed on the significance of plasma proteins but slightly below the lower levels of normal. In some persons, such a protein level may cause edema. This fact is due to postural effects, salt and fluid intake, anemia and environmental temperature."

Furthermore, with regard to nitrogen equilibrium, persons consuming low protein diets may be in nitrogen equilibrium if intake of carbohydrates and fats meets energy requirements. But low protein intake is not good because it does not allow for intercurrent illness or small inadvertent changes in the diet. Youmans [3] enlarged on this concept, as follows:

> The ordinary tests for serum protein measure only the concentration in the blood. Variations in the blood volume can affect the concentration so that changes in total circulating protein may occur without being recognized at the time of the test.

2. Stare, F. J., and Davidson, C. A.: Protein: Its Role in Human Nutrition, J. A. M. A. **127**:985 (April 14) 1945.

3. Youmans, J. B.: Clinical Detection of Protein Deficiency, J. A. M. A. **128**:439 (June 9) 1945.

This fact of recognized importance in acute states such as hemorrhage and shock, is often lost sight of in the slower changes of nutritional protein deficiency. Such a change in total circulating protein can be considered as an atrophy of the plasma.

Summing up this review, therefore, I may say that a diagnosis of protein deficiency does not depend on the finding of a low total serum

Fig. 1.—The legs of the patient in case 2, before protein balance was established.

protein or a reversal of the albumin-globulin ratio. And, further, a protein deficiency with the resulting clinical cutaneous manifestations of the type we have mentioned can be conceived of as occurring in a person of middle age or younger because of improper synthesis of plasma proteins by a diseased liver.

I shall demonstrate this point by reports of a few illustrative cases. First is an example of what I consider a true geriatric nutritional eczema.

CASE 1.—Mrs. H. M., a white woman aged 68, had an erythematopapulosquamous eczema of the legs and ankles. Underlying this was a definite pitting edema,

Fig. 2.—The legs of the patient in case 2, after protein balance was established.

with no varicosities. Questioning revealed that the patient lived practically on carbohydrate alone, partly from choice and partly because she could not eat meat, her dentition consisting of only a few carious snags. Initial serum protein determinations were as follows: 5.7 Gm. total protein, with 3.0 Gm. albumin and 2.7 Gm. globulin per hundred cubic centimeters.

She refused to get dental prosthesis but did agree to supplement her diet with protein hydrolysates. With fractional roentgen irradiation and an astringent anti-

septic paste applied locally, her condition improved remarkably. In six weeks, there was left only residual pigment and some thickening of the skin. The amounts of serum proteins reverted to normal.

CASE 2.—L. Y., a Negro aged 47, a clinic patient under treatment for latent syphilis, after a two week period of heavy drinking and light eating presented

Fig. 3.—The legs of the patient in case 3, before treatment.

himself in the clinic, in a highly nervous state and complaining of swelling and itching of his feet, ankles and legs. Their appearance was as is shown in figure 1.

He was hospitalized, and the results of laboratory studies were as follows: 8.56 Gm. total serum protein, with 2.26 Gm. albumin and 6.3 Gm. globulin per hundred cubic centimeters (determinations repeated twice with essentially the same results); sulfobromophthalein retention, 0 per cent; cephalin flocculation,

first test, 2 plus in twenty-four hours and 4 plus in forty-eight hours and, second test (a week later), negative in twenty-four hours and 2 plus in forty-eight hours.

After two weeks of a high vitamin, high protein diet, administration of supplemental protein hydrolysates by mouth, and application of an antipruritic shake lotion on the skin, the legs appeared as in figure 2. The serum globulin remained high for reasons I could not determine, but subsequent serum albumin determinations were normal. The patient has not been using alcohol since and has showed no recurrence.

Fig. 4.—The legs of the patient in case 3, after treatment.

I consider the following case an example of an acute hepatitis with temporary protein deficiency and dependent edema, with characteristic cutaneous consequences.

CASE 3.—G. W., a Negro woman aged 23, a social derelict who had been a persistently heavy drinker for some years, was admitted to the cutaneous clinic with edema and eczema of the legs below the knees. Figure 3 illustrates their appearance when I first saw the patient.

She gave a history of eight months' duration of the condition. On hospitalization, laboratory studies gave the following observations: 5.88 Gm. total serum

protein, with 3.75 Gm. albumin and 2.13 Gm. globulin per hundred cubic centimeters; cephalin flocculation, 4 plus in twenty-four hours, and sulfobromophthalein retention, 25 per cent.

The patient also had a microcytic anemia which was considered nutritional, and fluoroscopic studies showed changes in the small bowel consistent with avitaminosis.

After she had had three weeks on a high calorie diet, rich in proteins, supplemented by administration of protein hydrolysates by mouth, her legs appeared as in figure 4. Her serum proteins were back to normal, but tests for hepatic function were indicative of persistent hepatic impairment.

The following patient was considered by the department of medicine to have an example of active hepatitis, but with a well established portal cirrhosis.

CASE 4.—S. J., a white man aged 53, was a private patient whom I was treating for an erythrosquamous eczema of the lower two thirds of the legs. Edema was minimal, and there were no varicosities present. Roentgen irradiation and local treatment helped but did not clear up the eruption entirely. Finally, on questioning him, I found that he had consumed large amounts of alcohol daily for years. He was hospitalized, and some of the laboratory findings were as follows: 6.6 Gm. total serum protein, with 3.2 Gm. albumin and 3.4 Gm. globulin per hundred cubic centimeters; bromsulfalein retention, 50 per cent, and thymol turbidity, 8.5 units. Values in the glucose tolerance test were as follows: fasting, 88 mg.; first hour, 200 mg., and second hour, 141 mg.

In addition, careful examination by a medical consultant revealed a minimal ascites. All the findings established, I thought, a diagnosis of a full blown portal cirrhosis. Unfortunately, attempts to treat the patient were not fruitful because he would not cooperate in adhering to the diet, taking of medicines or abstaining from alcohol.

In addition to the direct effect of protein deficiency in the cutaneous manifestations we have been discussing, I should also like to call attention to its contributory effect in others. The studies of Mulholland and associates,[4] indicated that decubitus ulcers in bedridden patients are associated with hypoproteinemia. The recent work of Keim [5] and his associates also proposed this idea. It has been my experience, too, that adequate serum protein levels are effective in preventing decubitus ulcers. My associates and I have been studying serum proteins in persons with indolent leg ulcers of hemostatic origin. We have found a definite hypoproteinemia in several cases and believe that correction of this definitely gives an impetus to therapy. The following case is an instance:

CASE 5.—S. P., a white man aged 54, had varicose, hemostatic eczema of the legs and feet, of many years' duration. There was pronounced edema of the legs and feet, with the skin in some areas showing a dermatitis vegetans and in others

4. Mulholland, J. H.; Co Tui; Wright, A. M.; Vinci, V., and Shafiroff, B.: Protein Metabolism and Bed Sores, Am. J. Surg. **188**:1015 (Dec.) 1943.

5. Keim, H. L.; Frisch, D. C., and Palmer, A. E.: Plasma Proteins and Dermatitis, Arch. Dermat. & Syph. **58**:314 (Sept.) 1948.

a true lichen amyloidosis. The patient had had much treatment, including injections of the veins, with little success. The inner aspect of the right leg had a large ulcer, 8 by 4 inches (20 by 10 cm.), which had developed in recent months. We were suspicious of an epitheliomatous degeneration. Questioning revealed that the patient ate meat once or twice a week, and milk and eggs not at all, and that the bulk of his calories came from snacks of doughnuts and coffee. His serum proteins were as follows: 4.4 Gm. total, with 2.1 Gm. albumin and 2.3 Gm. globulin per hundred cubic centimeters.

Treatment consisted of local application of an astringent antiseptic paste, roentgen irradiation to the ulcer and the use of an elastic stocking. In addition, the patient was urged to partake of a protein-rich diet and administration of protein hydrolysates by mouth was prescribed. At the time of writing, after three months of this regimen the ulcer measured about 1½ by ¾ inches (4 by 2 cm.). The hypoproteinemia has been corrected. The legs were no longer edematous, but the cutaneous changes seemed to be irreversible.


## SUMMARY

I believe that these illustrations and laboratory findings speak for themselves in supporting the contention that lack of protein in the bodily economy is directly responsible for certain cutaneous conditions. The proteins most important in this regard are the plasma proteins, but a single determination of their concentrations in the blood may be misleading. In cases number 2 and 3, for instance, initial determinations of serum albumin were not very low, but at the time the blood specimens were taken the patients were in a pronounced state of dehydration resulting from alcoholic debauch. Clinical suspicion, in addition to information on preceding dietary status and alcoholic intake, led my associates and me to treat the patients as persons with protein deficiency, more than did the laboratory findings.

We are most interested in how clinical dermatologic thought has recently been slanted in the direction of this phase of protein metabolism and feel that our observations are worthy of report.


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## ABSTRACT OF DISCUSSION

DR. F. J. EICHENLAUB, Washington, D. C.: Dr. Guy's thesis, as I understand it, is that a change in colloidal chemistry occurs in the skin when there is a disturbance of the normal albumin balance, leading in certain cases to the development of eczematous eruptions. This disturbance may be caused by improper diet, particularly the neglect of proper protein ingestion, or it may be brought about by inability of the organism to assimilate proteins properly and maintain a balance, especially if the liver function is interfered with. He has presented a series of cases in which control of these factors has resulted in amelioration or cure of the eczema syndrome.

In a somewhat similar series of cases Dr. Ray Osbourn and I investigated the liver function. Our thought was that anything which led to edema of the skin predisposed to eczema in certain persons. Thus in some patients with edema from

varicose veins varicose eczema develops and in some patients with cardiovascular failure with edema eczema also develops. We felt that in our cases edema was produced by partial failure of liver function.

The comment that not all patients with cirrhosis of the liver, or, as in Dr. Guy's series, not all with protein deficiency, acquire eczema seems to me to be beside the point. After all, not all patients with varicose veins have ulcers or eczema. That there are undoubtedly other factors, does not militate against the varicose veins being one important factor in these patients. Dr. Guy has carried our thought one step further in the explanation of the cause in this group of cases. It is heartening to know that our younger colleagues are striving to probe deeper into the cause of this hitherto unexplained group of cases of eczema. I hope that Dr. Guy will continue his investigations in this field.

Dr. John H. Lamb, Oklahoma City: This question of protein metabolism cannot be brought up without consideration of the interrelation of hormonal activity and vitamins, particularly vitamin C and the B complex, in the utilization of proteins in the body. The pharmacologic action of the steroid hormones with reference to the powerful nitrogen retention action must be mentioned. The androgens, along with adequate protein therapy, have proved of particular value in cases of dermatomyositis. The androgens have been used because they seem to contain the most potent steroid action of any preparations on the market. Also the side reactions are safe, with the exception of hirsutism in the female. It is felt that the adrenal steroids are probably much more potent, but some of the side effects are more serious than are those associated with the use of the male hormone. Nevertheless, in androgen therapy one probably substitutes a steroid activity and supplants some that the adrenal gland has failed to provide. In another hopeless disease in which there has been some indication of adrenal insufficiency, pemphigus vulgaris, my associates and I have had some excellent results with a mixture of three steroid hormones: lipo-adrenal cortex (Upjohn), 40 rat units twice weekly; and testosterone propionate, 50 mg., and estradiol benzoate, 1 mg., the last mentioned two drugs being used on alternate days. With this is given 500 mg. of ascorbic acid daily; high protein therapy and adequate sodium chloride intake are also provided. There has been a remission in several cases of pemphigus vulgaris. The reaction to the steroid hormones in this disease is not a rapid procedure, and improvement is not seen for several months. We wish to report this treatment so that a trial may be carried out in various centers, particularly where large numbers of pemphigus cases are seen.

Dr. Michael G. Wohl, Philadelphia: In the course of investigations in Philadelphia General Hospital on the relation between antibody response and hypoproteinemia in patients with chronic illness, my associates and I, too, encountered a number of patients with chronic ulcers of the leg similar to the ones Dr. Guy has shown. These patients showed a serum albumin level of less than 4 Gm. per hundred cubic centimeters, which we consider the lower limit of normal. I think that the determination of serum albumin level gives a far more accurate expression of the existing state of protein depletion than the determination of total protein. The hypoproteinemia was due partly to an inadequate diet and partly to the disease itself. When such patients were tested for antibody response to a typhoid antigen by the Widal agglutination test and by the quantitative nitrogen antibody determination, they showed a lessened capacity to manufacture antibodies. When the diet was supplemented with either oral hydrolysates or protein concentrates, the antibody response was enhanced, and clinically the patients showed greater improvement than those that had not received supplementation.

Our patients did not tolerate hydrolysates. A number had diarrhea and other gastrointestinal upsets, and some of them, because of the ill tasting mixture, lost appetite for food. Therefore, we feel that protein concentrates are more acceptable by the patients.

It is important not only to supplement the protein but also to see that the total caloric intake is adequate, because, if the total caloric intake is insufficient, patients will use the protein supplementation for energy rather than for the manufacture of antibodies and for healing of the wounds.

DR. S. TASHIAN, Seattle: I am a proctologist. Members of my specialty see nearly all the cutaneous lesions that are manifested on the body. Conversely, lesions on other parts of the body may have a direct bearing on our local anorectal findings.

Twenty years ago I was impressed with the effect of proteins and amino acids on local lesions, especially on chronic ulcers. My thesis for a master's degree was entitled "Mobilization of Reticulo-Endothelial Cells as an Aid in Combating Infections." After many experiments, my associates and I found that by applying nutrient broth as wet dressings or by injecting it in and around chronic ulcers we could stimulate and increase the number of histiocytes and thus help heal chronic indolent ulcers. Histiocytes are essential for local tissue immunity and repair of wounds. Hundreds of such purulent lesions were cured before the time of antibiotics. I am delighted to hear Dr. Guy's magnificent work on systemic protein deficiency and its relation to cutaneous lesions. I wish to call attention to the direct or local use of proteins and protein derivatives, such as a nutrient broth which consists of 10 Gm. of Bactopeptone, 3 Gm. of meat extract, 8 Gm. of sodium chloride and 10 Gm. of glucose, in 1,000 cc. of distilled water, adjusted to $p_H$ 7.2 and autoclaved. It was Dr. F. P. Gay who, by injecting it into the pleura of rabbits, first demonstrated that nutrient broth stimulated and increased the number of histiocytes, thus producing active local immunity. It is well to remember the humble role of histiocytes in the defense mechanism of tissues and at the same time to supply the body with proper nourishment to carry on its normal healing processes, as Dr. Guy has so impressively brought to our attention.

DR. W. B. GUY, Pittsburgh: I want to thank all the discussers for their kind words. I was very interested in Dr. Lamb's observation of a retention of nitrogen when patients were under treatment with the male sex hormone.

Such an effect was noted in our city in patients under treatment for carcinoma of the breast, in which treatment testosterone was used. There was a pronounced retention of nitrogen as long as the patients were receiving that hormone.

In the matter of intolerance to hydrolysates by mouth, mentioned by Dr. Wohl, we have had the same difficulty. Frequently, patients cannot take it; it produces nausea and diarrhea, and the diarrhea, as such, does more harm than good because it further aggravates the protein deficiency. In those instances we have had to revert to the use of the concentrates administered by vein or to follow the procedure of the internists, who have expressed the belief that the best source of protein for a healthy person is plain, ordinary protein in its natural state, in the form of a high protein diet.

I was interested, also, in the observation of the antibody response, regarding the level of protein. Perhaps that is lack of immunity; local immunity further contributes to the damage in these patients, with edema and eczema of the legs below the knee. Perhaps lack of immunity allows secondary invaders to produce a suppurative purulent process.

# TRYPARSAMIDE AND BISMUTH SUBSALICYLATE IN THE TREATMENT OF EXPERIMENTAL SYPHILIS OF RABBITS

## Synergistic or Additive Activity

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A COMBINATION of penicillin injected intramuscularly and oxophenarsine hydrochloride (mapharsen®) administered intravenously has shown pronounced synergistic or additive effects in the chemotherapy of acute syphilitic orchitis of rabbits.[1] Similar results have been observed in combined treatment with penicillin and bismuth compounds administered intramuscularly.[2] Synergistic or additive effects have been observed also in combined treatment with penicillin given orally and oxophenarsine hydrochloride injected intravenously and intramuscularly and bismuth subsalicylate administered intramuscularly,[3] as they have been seen, likewise, in combined treatment with penicillin given by intramuscular injection and sodium iodide administered by oral and intravenous routes.[4] Since, however, combined treatment with penicillin injected intramuscularly and tryparsamide administered intra-

From the Research Institute of Cutaneous Medicine.

1. (*a*) Eagle, H.; Magnuson, H. J., and Fleischman, R.: The Synergistic Action of Penicillin and Mapharsen (Oxophenarsine Hydrochloride) in the Treatment of Experimental Syphilis, J. Ven. Dis. Inform. **27**:3 (Jan.) 1946. (*b*) Kolmer, J. A., and Rule, A. M.: Penicillin in the Treatment of Experimental Syphilis of Rabbits: II. The Synergistic or Additive Activity of Penicillin, Oxophenarsine Hydrochloride and Bismuth and Potassium Tartrate, Arch. Dermat. & Syph. **56**:179 (Aug.) 1947.

2. Kolmer and Rule [1b]; The Synergistic or Additive Activity of Chemotherapeutic Compounds, Am. J. M. Sc. **215**:136 (Feb.) 1948.

3. Kolmer, J. A., and Rule, A. M.: Penicillin in the Treatment of Experimental Syphilis of Rabbits: IV. The Synergistic or Additive Activity of Penicillin by Oral Administration with Oxophenarsine Hydrochloride ("Mapharsen") by Intravenous and Intramuscular Injection and Bismuth Salicylate by Intramuscular Injection, Arch. Dermat. & Syph. **57**:965 (June) 1948.

4. Kolmer, J. A., and Rule, A. M.: Penicillin in the Treatment of Experimental Syphilis of Rabbits: V. The Synergistic or Additive Activity of Penicillin Injected Intramuscularly with Sodium Iodide Administered Orally and Intravenously, Arch. Dermat. & Syph. **61**:49 (Jan.) 1950.

venously has shown much less evidence of synergistic or additive chemotherapeutic effects,[5] we have thought it advisable to determine whether or not combined treatment with bismuth compounds given by intramuscular injection and tryparsamide administered by the intravenous route has synergistic or additive effects in the treatment of experimental syphilis.

## METHODS AND MATERIALS

In our experiments all rabbits were inoculated intratesticularly with the Nichols-Hough strain of Treponema pallidum. Acute orchitis developed in all, with strongly positive results on dark field examinations about five or six weeks thereafter, when treatment was instituted. Dark field examinations were then made once a day for three days in succession and thereafter once a week over a total period of seventy days. At the expiration of that time the popliteal lymph nodes of all treated animals were inoculated into the testicles of fresh animals, which were kept under observation for a minimum of four months, when the results were evaluated.

Tryparsamide was dissolved in sterile distilled water and injected intravenously. Bismuth subsalicylate in oil (a suspension of bismuth subsalicylate, 0.13 Gm. per cubic centimeter in peanut oil, containing 3 per cent of chlorobutanol) was administered intramuscularly.

## RESULTS OBSERVED

*Single Doses of Bismuth Subsalicylate Injected Intramuscularly.*—As previously reported, the single minimal curative dose of bismuth subsalicylate in oil given by intramuscular injection in the treatment of acute syphilitic orchitis of rabbits was about 0.006 Gm. per kilogram of weight.[6] Closely similar results were observed in the present experiments, as shown in table 1. Single doses of 0.005 Gm. of bismuth subsalicylate per kilogram injected intramuscularly were spirocheticidal but did not produce complete or biologic cure. One of two rabbits given 0.008 Gm. per kilogram, however, showed biologic cure as, likewise, did all animals given 0.010 and 0.015 Gm. per kilogram.

*Single Intramuscular Injections of Bismuth Subsalicylate with Single Intravenous Injections of Tryparsamide.*—As previously reported, tryparsamide in a single dose of 0.05 Gm. per kilogram given by intravenous injection was ineffective in the treatment of acute syphilitic orchitis of rabbits, since the single minimal curative dose by this route of administration is about 0.6 Gm. per kilogram.[5]

5. Kolmer, J. A., and Rule, A. M.: Penicillin in the Treatment of Experimental Syphilis of Rabbits: VI. The Synergistic or Additive Activity of Penicillin Injected Intramuscularly and Tryparsamide Administered Intravenously, Arch. Dermat. & Syph., to be published.

6. Kolmer, J. A.; Brown, H., and Rule, A. M.: Studies in the Bismuth Therapy of Syphilis: I. A Comparative Study of the Toxicity and Therapeutic Activity of Bismuth Compounds Commonly Employed in the Treatment of Syphilis, Am. J. Syph., Gonor. & Ven. Dis. **23**:7 (Jan.) 1939.

This dose of 0.05 Gm. of tryparsamide per kilogram, which was about one-twelfth the single minimal curative dose of the compound, was administered intravenously at the same time that bismuth sub-

TABLE 1.—*Single Doses of Bismuth Subsalicylate Given by Intramuscular Injection in the Treatment of Acute Syphilitic Orchitis of Rabbits*

| No. | Dose, Gm. per Kg. | Results of Dark Field Examinations for T. Pallidum, Days * | | | | | | | | | | | | | Results of Transfer of Lymph Nodes |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 1 | 2 | 3 | 7 | 14 | 21 | 28 | 35 | 42 | 49 | 56 | 63 | 70 | |
| 1 | 0.001 | 4 | 1 | — | 4 | 4 | 4 | 4 | 4 | 3 | 3 | 4 | 4 | 4 | Positive |
| 2 | 0.001 | 4 | 1 | 1 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | Positive |
| 3 | 0.002 | 4 | 1 | — | — | — | — | — | — | 4 | 4 | 4 | 4 | 4 | Positive |
| 4 | 0.002 | 4 | — | — | — | — | — | — | — | 2 | 4 | 4 | 4 | 4 | Positive |
| 5 | 0.005 | 1 | — | — | — | — | — | — | — | — | — | 4 | 4 | 4 | Positive |
| 6 | 0.005 | 2 | — | — | — | — | — | — | — | — | — | 4 | 4 | 4 | Positive |
| 7 | 0.008 | 1 | — | — | — | — | — | — | — | — | — | — | — | — | Negative |
| 8 | 0.008 | 1 | — | — | — | — | — | — | — | — | — | — | — | — | Positive |
| 9 | 0.010 | 1 | — | — | — | — | — | — | — | — | — | — | — | — | Negative |
| 10 | 0.010 | 1 | — | — | — | — | — | — | — | — | — | — | — | — | Negative |
| 11 | 0.015 | 1 | — | — | — | — | — | — | — | — | — | — | — | — | Negative |
| 12 | 0.015 | 1 | — | — | — | — | — | — | — | — | — | — | — | — | Negative |

* After institution of treatment: 4 indicates large numbers of actively motile spirochetes per dark field; 3, 2 and 1 indicate smaller numbers of spirochetes per dark field, respectively; — indicates negative results on dark field examinations.

TABLE 2.—*Single Intramuscular Injections of Bismuth Subsalicylate with Single Intravenous Injections of Tryparsamide in the Treatment of Acute Syphilitic Orchitis of Rabbits*

| No. | Bismuth, Gm. per Kg. | Tryparsamide, Gm. per Kg. | Results of Dark Field Examinations for T. Pallidum, Days * | | | | | | | | | | | | | Results of Transfer of Lymph Nodes |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | 1 | 2 | 3 | 7 | 14 | 21 | 28 | 35 | 42 | 49 | 56 | 63 | 70 | |
| 1 | 0.001 | 0.050 | 4 | 4 | 1 | — | 4 | 4 | 4 | 4 | 3 | 3 | 4 | 4 | 4 | Positive |
| 2 | 0.001 | 0.050 | 4 | 4 | 2 | — | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | Positive |
| 3 | 0.002 | 0.050 | 4 | 4 | 1 | — | — | 4 | 4 | 4 | 3 | 4 | 3 | 4 | 4 | Positive |
| 4 | 0.002 | 0.050 | 4 | 4 | 1 | — | — | 3 | 4 | 4 | 3 | 3 | 3 | 4 | 4 | Positive |
| 5 | 0.008 | 0.050 | 4 | 1 | 1 | — | — | 4 | 4 | 3 | 3 | 4 | 4 | 4 | 4 | Positive |
| 6 | 0.008 | 0.050 | 4 | 1 | — | — | — | 2 | 4 | 4 | 3 | 3 | 4 | 4 | 4 | Positive |
| 7 | 0.004 | 0.050 | 1 | 1 | — | — | — | — | 4 | 4 | 4 | 3 | 3 | 4 | 4 | Positive |
| 8 | 0.004 | 0.050 | 2 | 1 | — | — | — | — | 4 | 4 | 3 | 4 | 3 | 4 | 4 | Positive |
| 9 | 0.005 | 0.050 | 1 | — | — | — | — | — | — | — | — | 4 | 4 | 4 | 4 | Positive |
| 10 | 0.005 | 0.050 | 1 | — | — | — | — | — | — | — | — | — | — | — | — | Positive |
| 11 | 0.008 | 0.050 | 1 | — | — | — | — | — | — | — | — | — | — | — | — | Negative |
| 12 | 0.008 | 0.050 | 1 | — | — | — | — | — | — | — | — | — | — | — | — | Negative |
| 13 | 0.010 | 0.050 | 1 | — | — | — | — | — | — | — | — | — | — | — | — | Negative |
| 14 | 0.010 | 0.050 | 1 | — | — | — | — | — | — | — | — | — | — | — | — | Negative |

* After institution of treatment: 4 indicates large numbers of actively motile spirochetes per dark field; 3, 2 and 1 indicate smaller numbers of spirochetes per dark field, respectively; — indicates negative results on dark field examinations.

salicylate in oil was injected intramuscularly in doses varying from 0.001 to 0.010 Gm. per kilogram in the treatment of fourteen animals. As shown in table 2, there was practically no evidence of synergistic

or additive effects. It is true that in this experiment there was complete or biologic cure for both rabbits which were given 0.008 Gm. of bismuth and 0.05 Gm. of tryparsamide as compared with biologic cure for but one of the two animals which were given 0.008 Gm. of bismuth subsalicylate per kilogram alone (table 1), but this slight evidence of additive activity of tryparsamide could well be within the range of experimental error under the conditions of the experiment.

*Multiple Intramuscular Injections of Bismuth Subsalicylate and Intravenous Injections of Tryparsamide.*—Multiple doses of tryparsa-

TABLE 3.—*Multiple Intramuscular Injections of Bismuth Subsalicylate and Intravenous Injections of Tryparsamide in Treatment of Acute Syphilitic Orchitis of Rabbits*

| | Bismuth Subsalicylate * | | Tryparsamide † | | Results of Dark Field Examinations for T. Pallidum, Days ‡ | | | | | | | | | | | | | Results of Transfer of Lymph Nodes |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| No. | Gm. per Kg. | Total | Gm. per Kg. | Total | 1 | 2 | 3 | 7 | 14 | 21 | 28 | 35 | 42 | 49 | 56 | 63 | 70 | |
| 1 | 0.0005 | 0.002 | .... | ... | 4 | 4 | 4 | 4 | — | — | — | — | 2 | 4 | 4 | 4 | 4 | Positive |
| 2 | 0.0005 | 0.002 | .... | ... | 4 | 4 | 4 | 4 | — | — | — | — | — | 4 | 4 | 4 | 4 | Positive |
| 3 | 0.001 | 0.004 | .... | ... | 4 | 4 | 1 | — | — | — | — | — | — | — | — | — | — | Positive |
| 4 | 0.001 | 0.004 | .... | ... | 4 | 4 | 2 | — | — | — | — | — | — | — | — | 4 | 4 | Positive |
| 5 | 0.002 | 0.008 | .... | ... | 4 | 4 | 1 | — | — | — | — | — | — | — | — | — | — | Negative |
| 6 | 0.002 | 0.008 | .... | ... | 4 | 3 | 1 | — | — | — | — | — | — | — | — | — | — | Negative |
| 7 | 0.003 | 0.012 | .... | ... | 4 | 4 | — | — | — | — | — | — | — | — | — | — | — | Negative |
| 8 | 0.003 | 0.012 | .... | ... | 4 | 4 | — | — | — | — | — | — | — | — | — | — | — | Negative |
| 9 | ..... | ..... | 0.05 | 0.4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | — | — | 4 | 4 | 4 | 4 | Positive |
| 10 | ..... | ..... | 0.05 | 0.4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | Positive |
| 11 | 0.0005 | 0.002 | 0.05 | 0.4 | 4 | 4 | 4 | 4 | — | — | — | — | — | — | 4 | 4 | 4 | Positive |
| 12 | 0.0005 | 0.002 | 0.05 | 0.4 | 4 | 4 | 4 | 3 | — | — | — | — | — | — | 4 | 4 | 4 | Positive |
| 13 | 0.001 | 0.004 | 0.05 | 0.4 | 4 | 4 | 1 | — | — | — | — | — | — | — | — | — | — | Negative |
| 14 | 0.001 | 0.004 | 0.05 | 0.4 | 4 | 4 | 2 | — | — | — | — | — | — | — | — | — | — | Negative |
| 15 | 0.002 | 0.008 | 0.05 | 0.4 | 4 | 4 | 1 | — | — | — | — | — | — | — | — | — | — | Negative |
| 16 | 0.002 | 0.008 | 0.05 | 0.4 | 4 | 3 | 1 | — | — | — | — | — | — | — | — | — | — | Negative |

* On the first, third, sixth and eighth days of treatment.
† Daily for eight days in succession.
‡ After institution of treatment: 4 indicates large numbers of actively motile spirochetes per dark field; 3, 2 and 1 indicate smaller numbers of spirochetes per dark field, respectively; — indicates negative results on dark field examinations.

mide and bismuth subsalicylate, however, have shown some degree of additive activity.

As previously reported, ten weekly intramuscular injections of bismuth subsalicylate in oil in a dose of 0.003 Gm. per kilogram (totaling 0.03 Gm.) were completely curative in the treatment of acute syphilitic orchitis of rabbits.[7] As shown in table 3, four intramuscular injections of bismuth subsalicylate in oil in a dose of 0.002 Gm. per kilogram

7. Kolmer, J. A.; Brown, H., and Rule, A. M.: Studies in the Bismuth Therapy of Syphilis: II. The Therapeutic Activity of Bismuth in Syphilis of Rabbits in Relation to Its Urinary Excretion, Am. J. Syph., Gonor. & Ven. Dis. **24**:415 (July) 1940.

(totaling 0.008 Gm.) given on the first, third, sixth and eighth days of treatment effected biologic cure in these experiments. However, when four intramuscular injections at these intervals were given along with daily intravenous injections of tryparsamide in a dose of 0.05 Gm. per kilogram for eight days in succession, the minimal curative dose of bismuth was reduced to 0.001 Gm. per kilogram (totaling 0.004 Gm.), which observation appears to show some evidence of additive or synergistic activity of tryparsamide.

## SUMMARY

1. In the treatment of acute syphilitic orchitis of rabbits the single minimal curative dose of bismuth subsalicylate in oil given by intramuscular injection was about 0.008 Gm. per kilogram of weight.

2. The intravenous injection of tryparsamide in a single dose of 0.05 Gm. per kilogram (about one-twelfth the single minimal curative dose) was without definite synergistic or additive activity when administered with single intramuscular injections of bismuth subsalicylate.

3. The minimal curative dose of bismuth subsalicylate administered by intramuscular injection on the first, third, sixth and eighth days of treatment was about 0.002 Gm. per kilogram, for a total of 0.008 Gm.

4. Daily intravenous injections for eight days in succession of 0.05 Gm. of tryparsamide per kilogram reduced the minimal curative dose of bismuth subsalicylate in oil administered on the first, third, sixth and eighth days of treatment to 0.001 Gm. (totaling 0.004 Gm.).

5. Under the circumstances it appears that tryparsamide in multiple doses has shown some degree of additive or synergistic activity when administered along with multiple doses of bismuth subsalicylate in the treatment of acute syphilitic orchitis of rabbits.

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# CUTANEOUS METASTASES SECONDARY TO CARCINOMA OF URINARY BLADDER

## Report of Two Cases and Review of the Literature

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AND
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CUTANEOUS metastases secondary to carcinoma of the bladder is of rare occurrence. In review of the literature we have found only 10 previously reported cases (the table). Two cases reported have not been included in this review: Leuenberger's case because of the question that the primary tumor might be a sarcoma and MacEwen's case because of the possibility of implant metastases in the skin following perineal urethrotomy. Higgins and Hausfeld have given an excellent review of this subject and asked for further reports of similar cases to add to the knowledge of carcinoma of the bladder.

*Cases of Cutaneous Metastases Secondary to Carcinoma of the Bladder Reported in the Literature*

| Author | Year Reported | Number of Cases |
|---|---|---|
| Kretschmer | 1922 | 1 |
| Geraghty | 1924 | 1 |
| Liljencrantz | 1930 | 1 |
| Fairley | 1931 | 1 |
| Rolnick and O'Neill | 1932 | 1 |
| Carcinoma Registry of the American Urological Association | 1934 | 2 |
| Atkinson | 1942 | 1 |
| Higgins and Hausfeld | 1948 | 2 |
| Total | | 10 |

In a review of the records of the Presbyterian Hospital of Chicago from Jan. 1, 1903 to Jan. 1, 1949 it was found that 453,891 patients were admitted to the hospital; a diagnosis of carcinoma was made for 11,265 of these patients. Cutaneous metastases were present in 33 (0.29 per cent) of them. The primary neoplasm was in the breast of 19 patients; in the rectum of 5; in the stomach in 2, and in the sigmoid colon, the cervix uteri, an ovary, a parotid gland and the thyroid gland in 1 each.

Read before the Chicago Urological Society, April 28, 1949.
From the Thomson Urological Fund and the Presbyterian Hospital of Chicago.

There were 1,114 patients with primary carcinoma of the bladder admitted to the hospital during this forty-six year period. There were 2 patients in this series with cutaneous metastases secondary to primary carcinoma of the bladder.

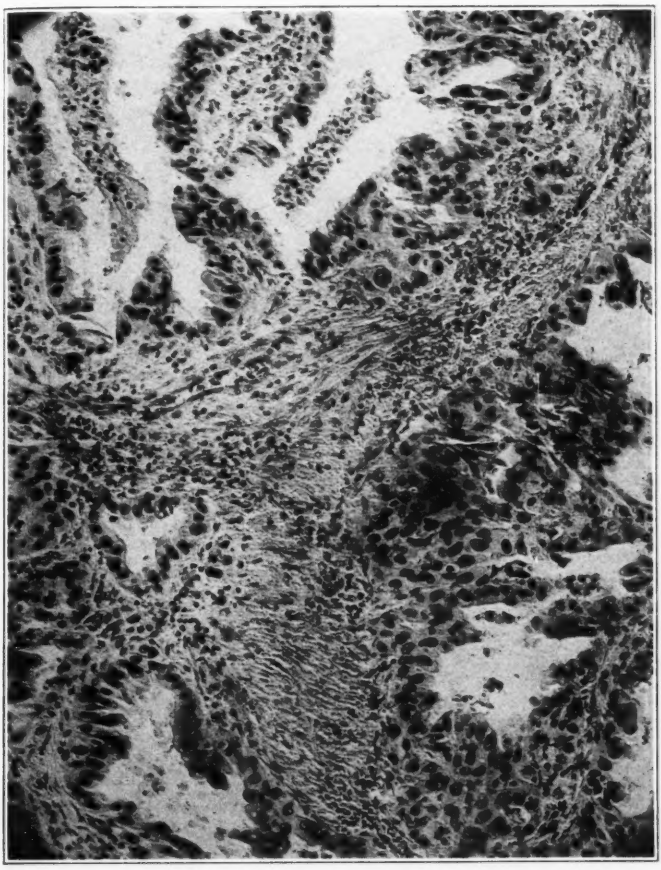

Fig. 1 (case 1).—Primary papillary carcinoma of the bladder with invasion of the stalk; × 100.

## REPORT OF CASES

CASE 1.—H. E. C., a white man aged 69, entered the Presbyterian Hospital on his tenth and final admission Oct. 26, 1941 on the service of Dr. Herman L. Kretschmer. His complaints were hematuria, frequency, dribbling and edema from the waist down. Six months prior to admission he had noted multiple nodules of the skin over the abdomen and right thigh.

*Previous History.*—The patient was first seen on Feb. 6, 1939. The diagnosis at this time was papillary carcinoma of the bladder, benign hypertrophy of the prostate gland and diverticulum of the bladder. The succeeding five admissions were for symptoms directly referable to the vesical carcinoma. Transurethral fulguration was performed on each of these admissions.

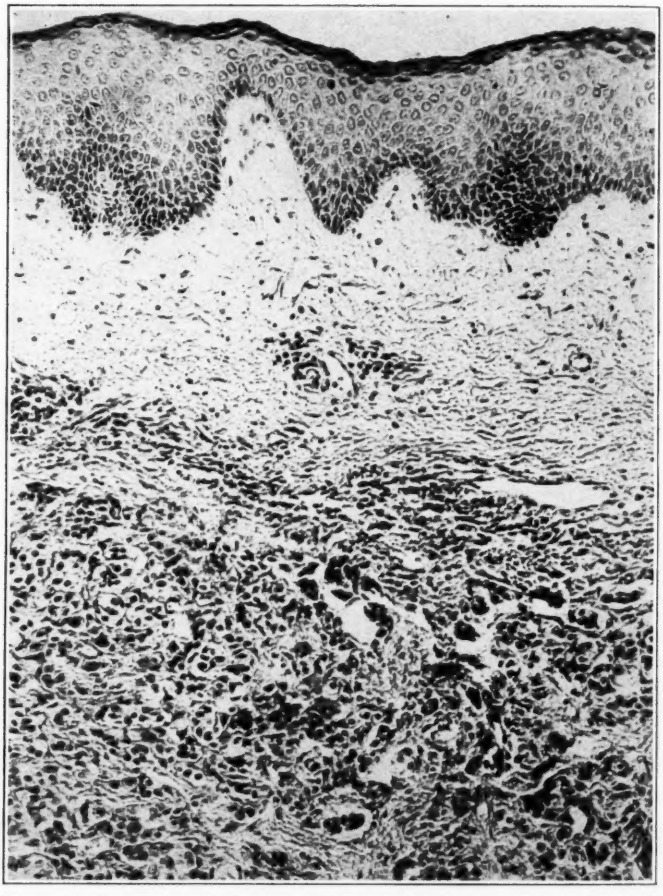

Fig. 2 (case 1).—Metastatic carcinoma of the bladder invading the cutis. Note the presence of tumor cells within the lymphatic channels; × 100.

The seventh hospital admission was on November 1, because of hematuria, frequency, nocturia and dysuria. Cystoscopy performed on the next day revealed a large papillary tumor in the dome of the bladder. On November 4, subtotal cystectomy was performed. Microscopic examination revealed a papillary carcinoma of the bladder (fig. 1). Thrombophlebitis of the left leg developed, but the patient responded well to treatment and was discharged on December 16.

The patient was readmitted to the hospital on June 26, 1940, again on October 26 of that year because of hematuria and of edema of the lower extremities secondary to lymphatic obstruction by metastatic extension from the carcinoma of the bladder. High voltage roentgen ray therapy in a total dose of 4,000 roentgen units (r) was given, with some improvement in the symptoms.

*Physical Examination.*—The examination revealed numerous hard, red, glossy, nontender nodules, 4 to 17 mm. in diameter, in the skin of the abdomen and right thigh. There was massive lymphedema of both lower extremities, the genitalia and the lower part of the abdomen.

The blood count revealed 3,900,000 erythrocytes, 11,800 leukocytes and 10.5 Gm. of hemoglobin. Urinalysis showed a specific gravity of 1.022, a 2 plus reaction for albumin and a negative reaction for sugar; on microscopic examination the urine appeared loaded with erythrocytes.

*Hospital Course.*—The patient was seen in consultation by Dr. O. S. Ormsby on Oct. 25, 1941, and he verified the diagnosis of metastatic carcinoma of the skin. A skin nodule was excised for microscopic study on October 29. Microscopic examination revealed irregular nodules of metastatic carcinoma composed of undifferentiated epithelial cells arranged in small sheets in the cutis. The cells were large and polyhedral with large pale vesicular nuclei and numerous mitotic figures (fig. 2).

Roentgen ray therapy (1,100 r) was given to the cutaneous lesions without benefit. There was gradual increase in the edema. Pain in the lower extremities increased and necessitated use of narcotics for relief. The patient was discharged unimproved on Nov. 30, 1941 and died at home March 9, 1942.

CASE 2.—A. R., a 69 year old white woman, was admitted to the Presbyterian Hospital in April 22, 1948 (service of Dr. William Kirby). Her complaints were gross hematuria, frequency and nocturia of one year's duration. One year prior to admission she noted multiple nonpainful nodules of the skin. Five weeks prior to admission she began having severe pain on voiding of urine and associated marked urgency, with voiding of urine every ten minutes.

*Physical Examination.*—The examination revealed an emaciated, white woman with icteric skin and scleras. The blood pressure was 136 systolic and 70 diastolic. There were multiple circumscribed, hard, nonindurated, nontender nodules in the skin of the face, neck, chest, back, abdomen, arms and thighs. Some of the nodules were fixed to the skin; others were fixed to underlying structures, and a few were freely movable beneath the skin. Examination of the chest revealed scattered areas of dulness and moist crepitant rales throughout both fields, especially marked over the right base. The heart was slightly enlarged to the left and soft systolic and diastolic murmers were heard at the apex. The abdomen was moderately distended and contained fluid. The liver was palpable 10 cm. below the right costal margin.

The blood count showed 3,200,000 erythrocytes, 7,100 leukocytes and 10.5 Gm. of hemoglobin. Urinalysis showed the presence of albumin (3 plus) and absence of sugar, and the microscopic examination revealed 250 erythrocytes and 300 leukocytes per cubic millimeter. Culture of the urine produced growths of Aerobacter aerogenes and an anhemolytic streptococcus.

The blood icterus index was 15 units, and the blood nonprotein nitrogen level was 40 mg. per hundred cubic centimeters.

*Hospital Course.*—On April 27, 1948 indwelling catheter drainage was instituted. It could not be maintained because of the passage of large amounts of necrotic tumor which blocked the catheter. On May 2, 1948 the patient became semicomatose but would respond to stimuli. On May 3, 1948 a skin nodule was

Fig. 3 (case 2).—Extension of a primary vesical carcinoma through the tunica muscularis of the bladder. Note the invasion of the lymphatic channels by the tumor cells; × 40.

excised from the region of the upper outer quadrant of the left breast for microscopic study. Microscopic study revealed a metastatic transitional cell carcinoma. Later in the day the patient became comatose and death occurred on the same day.

Autopsy was performed on the day of death by Dr. G. M. Hass. Gross examination revealed skin nodules as previously described that were attached to the skin and were firm in consistency and of grayish color.

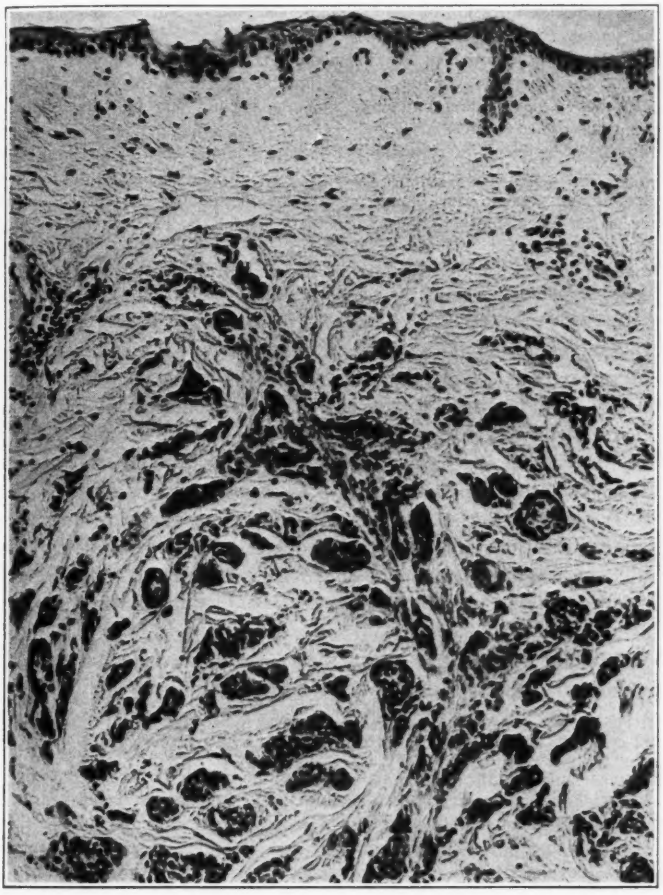

Fig. 4 (case 2).—Metastatic carcinoma of the bladder invading the cutis. Note the presence of tumor cells within the lymphatic channels; × 100.

The abdominal cavity contained 750 cc. of yellow-green fluid. The liver weighed 2,450 Gm., was hard and nodular and was extensively infiltrated with metastatic tumor tissue. The spleen weighed 300 Gm.; it cut with resistance, and the normal structures seemed to be entirely replaced by tumor tissue.

The bladder showed a large ulcerating tumor 8 cm. in diameter on the left lateral wall. The tumor had rolled, irregular edges and a red-brown necrotic base. The muscular layer was infiltrated by the tumor.

The splenic, pancreatic and retroperitoneal lymph nodes were enlarged and infiltrated with tumor tissue.

Microscopic study of the bladder tumor revealed a transitional cell carcinoma which had invaded the muscular layers and extended to the serosa of the bladder. There was marked invasion of the lymphatic channels within the bladder wall by the neoplastic cells (fig. 3).

Microscopic examination of the skin nodules revealed numerous nests of transitional cell carcinoma with many atypical mitotic figures in the lymphatic spaces beneath the epithelium and extending into the corium and into the underlying subcutaneous tissue (fig. 4).

Metastatic carcinoma of transitional cell type was also seen in the liver, spleen, lungs, thyroid gland, heart (in the myocardium and in a papillary muscle), aorta, pituitary gland, cervix uteri, bone marrow of the lumbar vertebrae, periaortic lymph nodes, splenic lymph nodes, pancreatic lymph nodes and the esophageal lymphatics.

Metastatic tumor was seen in the blood vessels of the thyroid gland, in the blood vessels of the adventitia of the aorta, and in the blood vessels within the pituitary gland.

## COMMENT

Most textbooks show the incidence of skin metastases in greatest frequency from primary tumors of the breast, uterus, stomach, lung, colon and pancreas. Ormsby states that skin metastases may occur secondary to primary neoplasms anywhere in the body and has an over-all incidence of 1 to 2.7 per cent.

Interesting in the subject of cutaneous metastases in carcinoma is the study of Liljencrantz, who at autopsy in 1,000 cases of carcinoma found metastases to the skin in 35 (3.5 per cent). In only 1 instance in 36 cases of primary carcinoma of the bladder did he find cutaneous metastases.

Willis and others have stated that secondary carcinoma metastases may reach the skin by means of the following routes:

1. Direct invasion from subadjacent growths.

2. Continuous extension along the lymphatics. This may assume several forms: the inconspicuous cutaneous lymphatic permeation which is rarely extensive and is detectable only on microscopic examination; nodules or plaques formed by outcropping from permeated deep fascial plexuses, reaching the dermis through vertical extension by tributary lymphatics and appearing in order of centrifugal direction from the primary tumor; cancer en cuirasse, which predominantly occurs secondary to carcinoma of the breast and is an extensive neoplastic thickening of the skin forming a continuous hard and rigid sheath.

3. Lymphatic embolism. This mechanism is responsible for a large portion of the outcropping metastatic tumors seen in the skin. There may be direct metastatic emboli to the skin, or the emboli may occlude deep fascial lymphatic plexuses or may lodge in the lymph nodes, with a resulting deviation of the lymph flow into

the cutaneous channels, which often occurs in a retrograde direction. The secondary tumors formed in this manner tend to remain circumscribed to the region of the primary tumor.

4. Hemic embolism. This mode of metastatic dissemination is responsible for a large group of secondary tumors of the skin, with widespread and relatively simultaneous appearance of the metastatic lesions.

Willis stated that metastases to the skin from the breast, bowel, and ovary are almost always lymph borne, whereas secondary skin metastases from the pancreas, kidney, uterus and bladder are usually blood borne. Secondary skin metastases of the stomach may be either blood borne or lymph borne.

In case 1 of our series metastases occurred in the skin of the abdomen and right thigh. The mode of transmission was partially lymphatic, in view of the evidence of metastatic involvement of the pelvic lymph channels and the involvement of the lymphatic channels of the corium in the secondary cutaneous lesion. However, case 2, with extensive metastatic lesions of the skin of the abdomen, thighs, anterior and posterior surfaces of the thorax, arms, neck and face represents an instance of blood-borne and lymph-borne dissemination of the metastatic lesions. Tumor cells were seen in the blood vessels of the thyroid gland, the pituitary gland and the adventitia of the aorta, as well as in the lymphatic channels of the bladder and the corium of the skin.

In Atkinson's case the metastatic skin lesion of the upper lip was blood borne. In the cases of Rolnick and O'Neill and Fairley, with metastases to the skin of the anterior walls of the abdomen and chest, it would be difficult to state definitely a mode of dissemination. Higgins and Hausfeld expressed the opinion that their cases represented both blood and lymph routes as the means of metastatic involvement of the skin.

In our 2 cases the patients lived eleven months and twelve months after the appearance of skin metastases. This does not concur with the observations of Grinevich or with the statement of Higgins and Hausfeld that when cutaneous metastases from carcinoma of the bladder make their appearance, death ensues within six months.

Ormsby has stated that the occurrence of skin metastases is generally indicative of rapid progression and early death, but he also expressed the belief that there are many exceptions to this rule. He cited slow-growing scirrhous carcinoma of the breast with cutaneous metastases and also the fact that a few patients have lived for years after metastases to the skin with melanoepithelioma have occurred. Willis has noted cases in which there have been widespread blood-borne metastases to the skin with the viscera little involved or entirely free of metastases. However, he did not comment on the relation of this form of the metastatic lesion to prognosis in the disease.

SUMMARY

Two cases of cutaneous metastases secondary to carcinoma of the bladder are reported. This brings the cases reported in the literature to a total of 12.

Secondary cutaneous metastases from carcinoma of the bladder are rare, occurring in only 2 of 1,114 cases (0.18 per cent) of primary carcinoma of the bladder during a forty-six year period.

Cutaneous metastasis in a case of primary carcinoma of the bladder indicates generally a rapid downhill course but cannot alone be the criterion for prognosis of early death.

BIBLIOGRAPHY

Anderson, W. A. D.: Synopsis of Pathology, St. Louis, C. V. Mosby Company, 1942.

Andrews, G. C.: Diseases of the Skin for Practitioners and Students, ed. 2, Philadelphia, W. B. Saunders Company, 1938.

Atkinson, R. C.: J. Urol. **48**:350, 1942.

Carcinoma Registry of the American Urological Association, J. Urol. **31**:423, 1934.

Ewing, J.: Neoplastic Diseases: A Treatise on Tumors, ed. 4, Philadelphia, W. B. Saunders Company, 1940.

Fairley, N. H.: Brit. M. J. **2**:983, 1931.

Geraghty, J. T., in Cabot, H.: Modern Urology, ed. 2, Philadelphia, Lea & Febiger, 1924, vol. 2, chap. 7.

Grinevich, V.: Urol. & Cutan. Rev. **45**:514, 1941.

Higgins, C. C., and Hausfeld, K. F.: J. Urol. **59**:879, 1948.

Kaufmann, E.: Pathology for Students and Practitioners, Philadelphia, P. Blakiston's Son & Company, 1929, vol. 3.

Kretschmer, H. L.: Surg., Gynec. & Obst. **24**:241, 1922.

Leuenberger, S. G.: Deutsche Ztschr. f. Chir. **14**:1, 1912.

Liljencrantz, E.: Cancer Handbook of the Tumor Clinic, Stanford University Calif., Stanford University Press, 1939.

MacEwen, cited by Milner.

McKee, G. M., and Cipollaro, A. C.: Cutaneous Cancer and Precancer: A Practical Monograph, New York, American Journal of Cancer, 1937, chap. 3.

Milner, R.: Arch. f. klin. Chir. **74**:1040, 1904.

Nuboer, J. F.: Virchow's Arch. f. path. Anat. **254**:70, 1925.

Ormsby, O. S., and Montgomery, H.: Diseases of the Skin, ed. 7, Philadelphia, Lea & Febiger, 1948.

Rolnick, H. C., and O'Neill, C. P.: Skin Metastases in Carcinoma of Bladder, Arch. Dermat. & Syph. (Nov.) **26**:882, 1932.

Willis, R. A.: The Spread of Tumours in the Human Body, London, J. & A. Churchill, Ltd., 1933, chap. 28.

# REEVALUATION OF WELTMANN SERUM COAGULATION REACTION IN SYPHILIS AND VARIOUS DERMATOSES

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THE WELTMANN serum coagulation reaction is a nonspecific laboratory test in which coagulation takes place in a certain number of mixtures of blood serum and varying concentrations of calcium chloride, in the presence of heat. The test is of value in differentiating exudative from fibrotic processes and in prognosticating the course and evolution of many diseases. It was originated by Oscar Weltmann [1] in 1930 and immediately found recognition in the world's medical literature. In this country, Kraemer [2] was the first to call attention to the test. Kraemer's article was soon followed by the work of Levinson and Klein,[3] Dees,[4] Scherlis and Levy [5] and many others in evaluation of the test from different aspects. However, only slight interest by the dermatologist has been shown in the Weltmann serum coagulation reaction, only one paper on the subject having appeared in the ARCHIVES OF DERMATOLOGY AND SYPHILOLOGY.[6]

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From the Graduate Hospital of the University of Pennsylvania, service of Dr. Donald M. Pillsbury.

Part of thesis submitted to the Faculty of the Graduate School of Medicine of the University of Pennsylvania in partial fulfilment of the requirements for the degree of Master of Medical Science for graduate work in dermatology and syphilology.

1. Weltmann, O.: Ueber die Spiegelung exudativ-entzündlicher und fibröser Vorgange im Blutserum, Med. Klin. **26**:240-245, 1930.

2. Kraemer, M.: The Weltmann Test in Diseases of the Liver, Am. J. Digest. Dis. & Nutrition **2**:14-16, 1935.

3. Levinson, S. A., and Klein, R. A.: Weltmann Serum Coagulation Reaction: Comparison with Sedimentation and with Clinical Findings in Pulmonary Tuberculosis, Am. Rev. Tuberc. **37**:200-237, 1938.

4. Dees, S. C.: A Clinical Study of the Weltmann Serum Coagulation Reaction, J. Pediat. **17**:44-52, 1940; An Experimental Study of the Weltmann Serum Coagulation Reaction, ibid. **17**:53-72, 1940.

5. Scherlis, S., and Levy, D. S.: Investigation into the Mechanism of the Weltmann Serum Coagulation Reaction: A Preliminary Report, Bull. John Hopkins Hosp. **2**:24-30, 1942.

6. Steiner, K.: Weltmann's Serum Coagulation Reaction in Cases of Dermatoses and of Syphilis, Arch. Dermat. & Syph. **46**:87-99 (July) 1942.

Weltmann noted that while normal serum was coagulated by boiling, no such reaction occurred when the serum was diluted with 50 parts of distilled water unless an electrolyte was added to it before boiling. The test, which he subsequently originated and which has been since known as the Weltmann serum coagulation reaction, is the process of mixing, in ten tubes, serum and 50 parts of calcium chloride solutions, arranged in order of decreasing concentrations from 0.1 to 0.01 per cent of calcium chloride and varying in each tube by 0.01 per cent, and heating the mixtures to boiling. Coagulation will occur in a certain number of the solutions. It was observed that the number of tubes in which flocculation appeared in normal serum was always constant and that serum in disease caused flocculation to stop to the left of normal, i. e., in the higher calcium chloride concentrations, if the underlying pathologic process was exudative, such as acute pulmonary tuberculosis. With serum of a patient with a fibrotic condition, such as cirrhosis of the liver, coagulation ended to the right of normal, i. e., in lower concentrations. It was also noted that with the serum in conditions in which both an exudative and a fibrotic process prevailed simultaneously flocculation stopped midway between right and left. The changes in a pathologic process from an inflammatory stage to a proliferative and finally to a normal stage were reflected in the pendulum-like behavior of the coagulation reaction: to the left of normal, then to the right and finally to a stationary position at the sixth tube. As fewer solutions are involved in the reactions in exudative conditions than in those in fibrotic conditions, the various bands formed were accordingly designated: narrowed (shortened) coagulation bands, or shift to the left, and widened (prolonged) coagulation bands, or shift to the right.

The test is nonspecific in that it points to the pathologic process and not to the etiologic factor. It has been compared in its behavior to other nonspecific tests of a similar character such as the complete blood count or the erythrocyte sedimentation rate but has been found more reliable because conditions other than the pathologic process to which other tests are sensitive do not affect the Weltmann reaction. Diurnal variation, normal pregnancy, albumin-globulin content of the blood, menstrual cycle, anemia and other physicochemical factors [7] which influence the erythrocyte sedimentation rate have no effect on the coagulation reaction. The same statement applies to factors which may influence the leukocyte count, such as drugs, exercise and digestion. Dees [4] in a survey of the literature found the following factors to have no effect on the outcome of the test: aging of the serum for one to two days, sunshine, irradiation, freezing, inactivation at 56 C., acacia,

7. Yardumian, K.: Physicochemical Factors Influencing Red Cell Sedimentation Rate, Am. J. Clin. Path. **7**:105-119, 1937.

$p_H$ of the serum and solution; bile; dehydrochloric acid (decholin®); the addition of barium, sodium and/or magnesium, calcium in the blood, serum calcium, various amino acids, some lipids, nonprotein nitrogen, total protein, albumin-globulin ratio, addition of albumin, fibrinogen, thrombin content, state of hydration, alkalinization, acidification, fasting and induced hyperpyrexia.

## TECHNIC OF THE WELTMANN SERUM COAGULATION REACTION

*Apparatus and Material.*—In the performance of the test, the following apparatus and material are required: refrigerator, centrifuge, hot water bath, serum rack, pipets (5 cc. and 1 cc. graduated in 0.1 cc.), 100 cc. volumetric flask, eleven wide-necked 100 cc. glass-stoppered bottles, Wassermann-sized test tubes, a few small beakers and flasks, crystalline calcium chloride ($CaCl_2:6H_2O$) and sufficient distilled water. All glassware is thoroughly washed and rinsed with distilled water before using. The ten dilutions are freshly made at weekly intervals.

*Preparation of the Solutions.*—The 10 per cent calcium chloride stock solution is prepared by dissolving 10 Gm. of the crystalline calcium chloride in sufficient distilled water to make 100 cc.

The ten solutions of calcium chloride in decreasing concentrations from 0.1 to 0.01 per cent and varying equally in each solution by 0.01 per cent are obtained by mixing in the first bottle 1 cc. of the stock solution with 99 cc. of distilled water. The same procedure is followed in preparing the rest of the solution, the amount of the stock solution in each successive bottle being decreased by 0.1 cc. and sufficient distilled water being added to make 100 cc. in each bottle.

*Procedure of the Test.*—Ten test tubes are placed in a serum rack and each filled with 5 cc. of the various calcium chloride solutions as indicated.

| Tube Number | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|---|---|---|---|---|---|---|---|---|---|---|
| Strength of solution of calcium chloride, per cent | 0.1 | 0.09 | 0.08 | 0.07 | 0.06 | 0.05 | 0.04 | 0.03 | 0.02 | 0.01 |

To each solution in the tubes 0.1 cc. of the centrifuged unhemolyzed serum is added, and the contents of each tube are thoroughly mixed by inversion. The rack of the tubes is immersed in a boiling water bath for fifteen minutes and then removed for observation of the reaction. The tube of the highest dilution in which coagulation is present is noted. A distinction is made between turbidity, which occurs in one or more tubes, and actual coagulation. The former is disregarded.

If more than six tubes are involved in the coagulation band, the reaction is considered a shift to the right. If only five or less show coagulation, it is considered a shift to the left. If six tubes comprise the coagulation band, the reaction is normal.

## RESULTS OF THE COAGULATION REACTION IN SYPHILIS

Table 1 presents the results of the coagulation reaction in a total of 80 tests, 1 in each case, the series being comprised of 67 cases of syphilis, 3 cases in which there were biologic false positive serologic reactions for syphilis and 10 in which the spinal fluids showed latent syphilis and neurosyphilis. The observations indicate, in direct ratio

to the progression of the disease, a decrease in the percentage of the narrowed coagulation bands and an increase in the percentage of widened coagulation bands. No widened coagulation bands were observed in the few cases in which there were biologic false positive serologic reactions for syphilis. A greater number of the last-mentioned type of case, the result depending on the underlying factor, would undoubtedly show more diverse reactions. The spinal fluid caused no coagulation in any of the solutions. This finding points to an agent other than the proteins in determination of the coagulation reaction, for the proteins are higher in quantity in the spinal fluid than in the blood.

The findings of widened coagulation bands in all stages of syphilis in this series correspond to the reports of Callaway,[8] Steiner [6] and

TABLE 1.—*Weltmann Serum Coagulation Reaction in Syphilis*

| | | | Tube, No. and Strength of Calcium Chloride Solution, per Cent | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Exudative Zone | | | | | Normal & | Fibrotic Zone | | | | | | |
| | No. of Cases | No. of Tests | 1 0.10 | 2 0.09 | 3 0.08 | 4 0.07 | 5 0.06 | 0.05 | 7 0.04 | 8 0.03 | 9 0.02 | 10 0.01 | Narrow Bands, per Cent | Normal Bands, per Cent | Wide Bands, per Cent |
| Serum | | | | | | | | | | | | | | | |
| Primary syphilis | 10 | 10 | .. | .. | .. | .. | 1 | 3 | 2 | 4 | .. | .. | 10.00 | 30.00 | 60.00 |
| Secondary syphilis | 14 | 14 | .. | .. | .. | .. | 1 | 2 | 4 | 7 | .. | .. | 7.14 | 14.28 | 78.57 |
| Latent syphilis | 30 | 30 | .. | .. | .. | .. | 1 | 4 | 9 | 16 | .. | .. | 3.33 | 13.33 | 83.33 |
| Neurosyphilis (asymptomatic) | 5 | 5 | .. | .. | .. | .. | .. | .. | 3 | 2 | .. | .. | ..... | ..... | 100.00 |
| Neurosyphilis (symptomatic) | 5 | 5 | .. | .. | .. | .. | .. | .. | 2 | 3 | .. | .. | ..... | ..... | 100.00 |
| Cardiovascular syphilis | 3 | 3 | .. | .. | .. | .. | .. | .. | 1 | 2 | .. | .. | ..... | ..... | 100.00 |
| Biologic false positive reactions | 3 | 3 | .. | .. | .. | .. | 1 | 2 | .. | .. | .. | .. | 33.30 | 66.7 | ..... |
| Spinal fluid | | | | | | | | | | | | | | | |
| Neurosyphilis and latent syphilis | 10 | 10 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | ..... | ..... | ..... |

Sicher and Wiedmann.[9] Pellegrini and Barsini [10] obtained widened bands in early syphilis. Longo,[11] Kretz and Kudlac,[12] and Teufl [13]

8. Callaway, J. L.: Weltmann Serum Coagulation Reaction in Syphilis, Am. J. Syph., Gonor. & Ven. Dis. **31**:216-285, 1945.

9. Sicher, G., and Wiedmann, A.: Das Koagulationsband von Weltmann bei Syphilis, Med. Klin. **30**:1664-1666, 1934.

10. Pellegrini, M., and Barsini, G.: Il comportamento ed il significato della sieroreazione di Weltmann in alcuni stati morbosi: Ricerche sul comportamento della soglia elettrolitica della coagulo-flocculazione al calore degli essudati, transudati e del liquido cefalo-rachidiano normale e patologico, Minerva med. **1**:154-162, 1934.

11. Longo, N.: La siero-reasione di Weltmann delle mallatie nervose e mentali, Boll. Soc. med.-chir., Catania **2**:827-831, 1934.

12. Kretz, J., and Kudlac, O.: Untersuchungen über das Verhalten der Serumeiweisskörper mittels der Weltmannschen Reaktion, Ztschr. f. klin. Med. **127**:590-608, 1934.

13. Teufl, R.: Der diagnostische Wert der Serumkoagulation nach Weltmann, Wien. Arch. f. inn. Med. **29**:37-52 and 297-330, 1936.

found widened bands in neurosyphilis. Balan [14] reported a few narrowed bands in early spyhilis. Midana and Leone [15] found narrowed bands in 52 per cent of their cases of early syphilis and normal and widened bands in a few cases of late syphilis. Pastinszky and Füsthy [16] obtained a shift to the left in 58 per cent of the cases of primary syphilis, 52 per cent of secondary syphilis, 20 per cent of latent syphilis and 4 per cent of gumma. They found a shift to the right in 12 per cent of the cases of primary syphilis, 14 per cent of secondary syphilis, 5 per cent of latent syphilis and 64 per cent of gumma. They explained their observations on the basis of tissue exudation and liver damage which are present in this disease. However, that explanation should be accepted with reservations, for acute syphilis, from the appearance of the chancre to the disappearance of the secondary lesions, is characterized by little or no tissue destruction, and, according to Moore,[17] clinical evidence of hepatic damage is observed not oftener than in 1 out of 1,000 cases in recently infected patients and in less than 1 out of 200 in cases of late syphilis and at necropsy.

The broadened coagulation bands in late syphilis and neurosyphilis are explained on the basis of fibrosis by which these stages are characterized. But how is one to account for the same observation in early acute syphilis? The most plausible explanation is that the cellular and biochemical mechanism concerned in fibrosis becomes manifest in the early stages of syphilis.[18] The process begins with the local defense by the lymphocytes and plasma cells against the invasion by Treponema pallidum in the perivascular lymph spaces of the site of primary inoculation and other foci of ectodermal origin. These cells, especially the plasma cells, are rich in lipids, and the same characteristic is found in the treponeme. As the result of the interaction of the host's defenses and the parasite, there is a great deal of destruction of parasites and cellular elements, with the resulting liberation of decomposed lipoprotein material in the circulating fluid. Thus, from the very beginning of a syphilitic infection there is a tendency on the part of the local immunologic process to proceed in the direction of fibrosis. This is

14. Balan, E.: Das Koagulationsband von Weltmann bei Syphilis, Arch. f. Dermat. u Syph. **173**:483-494, 1936.

15. Midana, A., and Leone, R.: La reazione di Weltmann in dermatologia, Dermosifilografo **9**:494-503, 1934.

16. Pastinszky, S., and Füsthy, E.: Examinations of Syphilitic Patients with the Weltmann Reaction, Acta dermat.-venereol. **27**:267-274, 1947.

17. Moore, J. E.; Kemp, J. E., and others: The Modern Treatment of Syphilis, ed. 2, Springfield, Ill., Charles C Thomas, Publisher, 1941, pp. 304 and 305.

18. Burke, E. T.: Role of Iodine in the Therapy of Syphilis, Arch. Dermat. & Syph. **32**:404-412 (Sept.) 1935.

inevitable because of the production of unsaturated lipid radicals, which, according to Jobling and Petersen,[19] are the main biologic features of syphilis.

The plasma cell which is constantly present in all stages of syphilis is present in other chronic inflammatory diseases characterized by fibrosis, like the infectious granuloma of tuberculosis and rhinoscleroma, and is absent in acute suppurative diseases. It is considered by Unna as the mother cell of the fibrous corium; i.e., it is of connective tissue origin.[20]

### COAGULATION REACTION IN VARIOUS DERMATOSES

Table 2 shows the coagulation reactions of 142 serums drawn from 130 patients with 38 types of dermatoses. The data indicate a shift to the left in 27.5 per cent of all tests, normal reactions in 27.5 per cent and a shift to the right in 45 per cent. The following dermatoses are of interest both because of the coagulation reaction and because of their course and evolution. A patient with Sulzberger and Garbe disease (exudative, discoid and lichenoid chronic dermatitis) showed at one time a narrowed reaction band, and, at another time, a widened band. These reactions are to be expected in such an unstable disease, which is characterized by exudation, lichenification, granuloma fungoides–like infiltrations and urticarial lesions occurring alone or in combination. Similar shifts from the left to the right were obtained on improvement in the course of pemphigus and the bullous form of erythema multiforme. Thus, the test is of no value in differentiating the latter disease from the former. One has to resort to the history and clinical course in reaching a diagnosis. The serum of a patient with lymphosarcoma showed on two occasions a shift to the left. The interesting feature of the case was that the primary complaint of the patient was centered on erythema nodosum–like lesions on her lower extremities. The history, physical examination and roentgenologic studies revealed no demonstrable cause for the lesions. The bilateral femoral adenopathy, like the elevated temperature, was considered at first to be part of the same process. The laboratory examination disclosed mild leukocytosis, secondary anemia, high sedimentation rate and a narrowed coagulation band. The cutaneous disorder and anemia resolved and the temperature and leukocyte count reverted to normal

19. Jobling, J. W., and Petersen, W. F.: The Therapeutic Effect of Iodin, J. A. M. A. **63**:1930-1931 (Nov. 28) 1914; The Therapeutic Action of Iodin, Arch. Int. Med. **15**:286-302 (Feb. 15) 1915; Study of the Ferments and Antiferments of the Body and Their Relation to Certain Diseases, Bull. Johns Hopkins Hosp. **26**:356-365, 1915.

20. MacLeod, J. M. H., and Muende, I.: Practical Handbook of the Pathology of the Skin, ed. 2, New York, Paul B. Hoeber, Inc., 1940, pp. 131 and 147.

after blood transfusions and administration of sulfadiazine. However, the femoral adenopathy, sedimentation rate and the coagulation reaction remained unchanged. The diagnosis of lymphosarcoma was finally established by a biopsy of the femoral gland. Cairns and Brandenstein [21] found narrowed coagulation bands in 73.4 per cent of 79 cases of malignant tumors; prognosis in those cases with a 0.0 per cent band

TABLE 2.—*Weltmann Serum Coagulation Reaction in Various Dermatoses*

| | | | Tube No. and Strength of Calcium Chloride Solution, per Cent | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Exudative Zone | | | | | Normal | Fibrotic Zone | | | |
| | No. of Cases | No. of Tests | 1 0.10 | 2 0.09 | 3 0.08 | 4 0.07 | 5 0.06 | 6 0.05 | 7 0.04 | 8 0.03 | 9 0.02 | 10 0.01 |
| Disease | | | | | | | | | | | | |
| Atopic dermatitis | 6 | 6 | .. | .. | .. | .. | .. | 2 | 4 | .. | .. | .. |
| Chancroid | 3 | 3 | .. | .. | 2 | 1 | .. | .. | .. | .. | .. | .. |
| Contact dermatitis | 5 | 5 | .. | .. | .. | .. | 1 | 2 | 2 | .. | .. | .. |
| Dermatitis herpetiformis | 2 | 2 | .. | .. | .. | .. | 1 | 1 | .. | .. | .. | .. |
| Dermatofibroma | 2 | 2 | .. | .. | .. | .. | .. | 2 | .. | .. | .. | .. |
| Eczematoid dermatitis | 10 | 10 | .. | .. | .. | .. | 1 | 3 | 4 | 2 | .. | .. |
| Erysipelas | 1 | 1 | .. | .. | 1 | .. | .. | .. | .. | .. | .. | .. |
| Erythema multiforme | 3 | 3 | .. | .. | .. | .. | 1 | .. | 2 | .. | .. | .. |
| Erythema multiforme bullosum | 2 | 4 | .. | 2 | .. | .. | 1 | 1 | .. | .. | .. | .. |
| Erythroderma exudativum | 2 | 4 | .. | 2 | 1 | .. | .. | 1 | .. | .. | .. | .. |
| Erythema nodosum | 3 | 4 | .. | .. | .. | 1 | 2 | 1 | .. | .. | .. | .. |
| Fungous infections | 5 | 5 | .. | .. | .. | .. | .. | 3 | 2 | .. | .. | .. |
| Herpes zoster | 3 | 3 | .. | .. | .. | .. | 3 | .. | .. | .. | .. | .. |
| Hodgkin's disease | 1 | 2 | .. | .. | .. | 1 | .. | 1 | .. | .. | .. | .. |
| Hodgkin's disease of the skin | 1 | 1 | .. | .. | .. | .. | 1 | .. | .. | .. | .. | .. |
| Ichthyosis | 4 | 4 | .. | .. | .. | .. | .. | .. | 2 | 2 | .. | .. |
| Idiopathic multiple pigmented sarcoma | 2 | 2 | .. | .. | .. | .. | .. | .. | .. | 2 | .. | .. |
| Infectious eczematoid dermatitis | 5 | 5 | .. | .. | .. | 1 | 2 | 2 | .. | .. | .. | .. |
| Leiner's erythroderma desquamativum | 1 | 2 | .. | .. | .. | 1 | .. | .. | 1 | .. | .. | .. |
| Leukemia, chronic | 1 | 1 | .. | .. | .. | .. | .. | .. | 1 | .. | .. | .. |
| Lichen planus | 5 | 5 | .. | .. | .. | .. | .. | 1 | 1 | 2 | 1 | .. |
| Lichen simplex chronicus | 4 | 4 | .. | .. | .. | .. | .. | 2 | 2 | .. | .. | .. |
| Lupus erythematosus, discoid | 3 | 3 | .. | .. | .. | .. | .. | 1 | 2 | .. | .. | .. |
| Pemphigus | 2 | 4 | .. | .. | 2 | .. | 2 | .. | .. | .. | .. | .. |
| Pigmented purpuric lichenoid dermatitis | 1 | 1 | .. | .. | .. | .. | .. | .. | 1 | .. | .. | .. |
| Pityriasis rosea | 5 | 5 | .. | .. | .. | .. | 1 | 2 | 2 | .. | .. | .. |
| Poikiloderma vasculare atrophicans | 2 | 2 | .. | .. | .. | .. | .. | .. | 2 | .. | .. | .. |
| Pruritis, generalized | 5 | 5 | .. | .. | .. | .. | .. | 2 | 2 | 1 | .. | .. |
| Pruritis, localized | 5 | 5 | .. | .. | .. | .. | .. | 3 | 2 | .. | .. | .. |
| Psoriasis | 10 | 10 | .. | .. | .. | .. | .. | 1 | 4 | 4 | 1 | .. |
| Rosacea | 2 | 3 | .. | .. | 1 | .. | .. | 1 | 1 | .. | .. | .. |
| Sarcoma, lymphatic | 1 | 2 | .. | .. | 1 | 1 | .. | .. | .. | .. | .. | .. |
| Seborrheic dermatitis | 6 | 6 | .. | .. | .. | .. | 2 | 3 | 1 | .. | .. | .. |
| Stasis dermatitis | 5 | 5 | .. | .. | .. | .. | .. | 3 | 2 | .. | .. | .. |
| Sulzberger and Garbe disease | 1 | 2 | .. | .. | .. | 1 | .. | .. | 1 | .. | .. | .. |
| Thrombophlebitis | 3 | 3 | .. | .. | .. | 2 | 1 | .. | .. | .. | .. | .. |
| Urticaria, acute | 5 | 5 | .. | .. | .. | .. | 1 | 1 | 2 | 1 | .. | .. |
| Urticaria, chronic | 3 | 3 | .. | .. | .. | .. | .. | 1 | 2 | .. | .. | .. |

was always hopeless. Leiner's erythroderma desquamativum caused a shift to the left in the exudative stage and a shift to the right in the dry exfoliative stage. Glaser and Markson,[22] in a similar case in which there was a fatal termination, found an irreversible hypoproteinemia.

21. Cairns, A. B., and Brandenstein, L.: Weltmann Reaction in Malignant Diseases, Texas State J. Med. **26**:22-26, 1940.

22. Glaser, K., and Markson, S. M.: Value of Serum Protein Determination in Cases of Suspect Erythroderma Desquamativum of Newborn, J. Pediat. **26**:367-373, 1945.

They advocated determinations of serum protein in Leiner's disease as prognostic and therapeutic aids. The same suggestion applies to the coagulation reaction. In a case of rosacea complicated by a severe staphyloderma of the face caused by the release of a focus of infection after five abscessed teeth were removed at one sitting, there was a shift to the left. A narrowed coagulation band was found in a case of an exudative erythroderma, the result of vaccination against smallpox in a patient with psoriasis. Hodgkin's disease showed a shift to the left which changed to the right after nitrogen mustard therapy. Thus, the test is of value from a therapeutic aspect.

In general, in dermatoses of an infectious, acutely inflammatory and exudative character which are widespread or of a small area but sufficiently severe to cause an elevation of temperature, there appears a shift to the left in the Weltmann reaction. In those characterized by chronicity, proliferation and degeneration, unless a small area is involved in the process, there appears a shift to the right.

### MECHANISM OF THE WELTMANN SERUM COAGULATION REACTION

The mechanism of the phenomenon of the coagulation reaction is still obscure. Weltmann's test is based on the observation by others[23] that human serum coagulates at different temperatures with various types of diseases and is influenced by the electrolytic concentrations of the serum and diluent. Weltmann noted that when an electrolyte in a series of decreasing concentrations is added to the serum before boiling the intensity of coagulation is proportional to the concentration of the electrolyte and the threshold of flocculation is determined by the nature of the serum in the various diseases. However protein quantitatively,[11] although a minimal amount is required for the test, has no effect on the range of coagulation. Many diseases with identical quantities of protein may vary in their coagulation bands, as is shown in lobar pneumonia and cirrhosis of the liver. Often a 1 : 100 dilution of serum may show a wider coagulation band than a 1 : 50 dilution of the same serum. The belief that the reversal of the albumin-globulin ratio was necessary for a shift to the left in the reaction has been disproved by the varying coagulation reactions in the many diseases in which a reversal of the albumin-globulin ratio is a characteristic

23. Aronstein, B.: Ueber die Darstellung salzfreier Albuminlosungen vermittelst der Diffusion, Arch. f. d. ges. physiol. **8**:75-94, 1874. Hugo, K.; Ein Beitrag zur Theorie der antagonistischen Ionenwirkungen der Erdalakalien auf das Pflanzenplasma, Biochem. Ztschr. **167**:25-37, 1926. Handovsky, H.: Untersuchungen über die Zusammensetzung des Blutserums und ihre Bedeuting für Giftwirkungen, Arch. f. d. ges. Physiol. **210**:35-69, 1925.

feature. Kiriakis [24] stated that while globulin may increase the amount of the flocculus, it does not affect the coagulation band.

Scherlis and Levy [5] in fractionation experiments demonstrated an inverse relation between the percentage of alpha-globulin in the serum and the coagulation bands; when the former was higher, the latter was narrowed, or vice versa. They believed that the alpha-globulin was a decisive factor in the determination of the coagulation reaction. A relation between the $p_H$ of the serum and the coagulation bands was established by Levinson and Klein.[3] They noted narrowed coagulation bands when the $p_H$ of the serum shifted to the alkaline side and widened coagulation bands when the $p_H$ of the serum shifted to the acid side, but they attributed no significance to that relation. They expressed the belief that both phenomena are merely reflections of the same underlying process and that the $p_H$ of the serum and diluent do not influence the coagulation reaction. The effect of calcium on the test was investigated by Kaiser,[25] who found that the coagulation bands were slightly widened for a short period by the intravenous administration of calcium. He attributed the widened bands obtained with hemolyzed serum to the liberation of calcium from the red cells. Dees [4] in original experiments demonstrated the failure of coagulation bands to occur when calcium was removed from the animal system by the addition of sulfonated oil, which has an affinity for calcium. However, it was observed that serum calcium values bear no relation to the length of the bands [26] and that ions other than calcium may aid in forming coagulation bands. Dees also obtained widening of the bands by the addition of fatty acids in vitro and suggested that in clinical conditions the level of the fatty acids and the amount of their unsaturation may be a factor which greatly influences the coagulation reaction. An allergic factor can hardly be considered because in allergic diseases there are normal reactions unless an infectious process is present in their background.[27]

## COMMENT

After reconsideration of the phenomenon of the mechanism of the Weltmann serum coagulation reaction, it becomes obvious that the serum protein, serum calcium and calcium in solution are essential in the mechanism of the test. The significance of protein is borne out

24. Kiriakis, L.: Versuche zur Klarung der Entstehung des Weltmannschen Koagulationsbands, Klin. Wchnschr. **14**:828-829, 1935.

25. Kaiser, T.: Beitrag zur Weltmannschen Serumkoagulation bei Lungentuberkulose, Beitr. z. Klin. d. Tuberk. **83**:271-279, 1933.

26. Pongor, F.: Ueber die Weltmannsche Reaktion, Ztschr. f. Tuberk. **73**:193-197, 1935.

27. Dees, S. C.: The Value of Weltmann Serum Coagulation Reaction in Allergic Diseases, South. M. J. **34**:586-592, 1941.

by the protein nature of the coagulum and by the fact that protein has the property of being coagulated by heat. The importance of calcium is shown by the failure of coagulation bands to form when calcium is removed from the animal system and by one's inability to obtain flocculation in a 1 : 50 dilution without the electrolyte. However, in view of the fact that some diseases with identical serum proteins and calcium values may vary in their coagulation reaction, it becomes evident that other factors are involved in the mechanism of the test. Thus, according to the rest of the evidence available, the missing link in the mechanism of the Weltmann reaction is either in the alpha-globulin or in the fatty acids. Regarding the role of the alpha-globulin, one may assume a skeptical attitude because of the lack of supporting evidence. Furthermore, it is likely that, in their relation to the test, the alpha-globulin values, like the $p_H$ of the serum, are merely reflections of the same underlying process and do not influence the outcome of the test. On the other hand, in addition to the experimental proof, there is sufficient clinical evidence for one to consider the fatty acids the determining factor in the reaction.

The following observations elucidate the role of fatty acids, which in some manner determine the character of some diseases:

Syphilis is characterized by fibrosis, and the same feature is noted in the resolution of a pulmonary tuberculous process. According to Jobling and Petersen,[19] the unsaturated fatty acids present in these diseases have a decisive inhibitory action on the proteolytic ferments which under normal conditions inhibit formation of excessive fibrous tissue deposits. So universally has this been true that many pathologic conditions, notably the gumma or tubercle, are caused by the presence of the fatty acids, and, if the latter are rendered inactive by their saturation with iodine, these lesions rapidly soften under the influence of the liberated ferments.

Klotz [28] supposed that in some way fats, through their decomposition into fatty acids and formation of calcium soaps, which later give rise to calcium carbonates and phosphates, constitute the basis of calcification. (Mechanism: Neutral fats which are compounds of fatty acids and glycerol are broken up; the fatty acids thus liberated, in combination with an alkali of potassium or sodium, form a soluble soap. The alkali in the ensuing process is replaced by calcium, with the formation of an insoluble soap. Finally, there is a gradual disappearance of the fatty acid radical, and it is replaced by phosphates and carbonates.)

28. Klotz, O.: Studies upon Calcareous Degeneration, J. Exper. Med. **7**:633-675, 1905.

Wells [29] claimed that the chemical composition of calcinosis is approximately the same as that of calcified structure elsewhere in the body: calcium phosphate, 86 per cent; calcium carbonate, 13 per cent, and magnesium phosphate, 1 per cent.

Weidman and Shaffer [30] in their report of a case, in which a fatty change preceded the calcareous formation, made the following statement:

> Klotz's idea is that in the process of calcification there is a preliminary fatty metamorphosis of tissue, and that the final calcification comes about through a series of intermediate changes in which soap figures. His theory has been attacked, it is true, by no less an authority than Wells, among others, but it is sound clinically, has been supported experimentally and needs little more proof than the direct evidence of cases such as ours. We feel that our case materially strengthens Klotz's position in the general pathology of calcifications.

Langmead [31] expressed conviction that calcinosis, generalized scleroderma, dermatomyositis and myositis fibrosa are all manifestations of one disease and that most frequent is the association of sclerodactylia with calcinosis.

The previous remarks show, in a number of diseases, not only the function of the fatty acids in determining fibrosis and calcification but also their affinity for calcium. As calcium is essential in the mechanism of the coagulation reaction, it is logical to assume that the fatty acids, by reason of their deciding influence in the pathogenesis of fibrosis and calcification, reflect similarly in a serologic test system which discloses these processes.

The role of the fatty acids in determining the outcome of the coagulation test is further lent credence by the following observations: Fatty acid content of the blood is increased in anemia, leukemia, nephritis and diabetes.[32] These diseases are characterized by widened coagulation bands. Stoesser and McQuarrie [33] studied the levels of plasma lipids during the acute illness and during convalescence in 27 cases. They found a definite lowering of the levels at the height of the disease compared with the levels obtained during convalescence. The acute

29. Wells, H. G.: Chemical Pathology, ed. 5, Philadelphia, W. B. Saunders Company, 1925.

30. Weidman, F. D., and Shaffer, L. W.: Calcification of the Skin, Including the Epiderm, in Connection with Extensive Bone Resorption, Arch. Dermat. & Syph. **14**:503-532 (Nov.) 1926.

31. Langmead, F. S.: Relationship Between Certain Rare Diseases, Arch. Pediat. **40**:112-120, 1923.

32. Peters, J. P., and Van Slyke, D. D.: Quantitative Clinical Chemistry, Baltimore, Williams & Wilkins, 1931, vol. 1, pp. 247 and 254.

33. Stoesser, A. V., and McQuarrie, I.: Influence of Acute Infection and Artificial Fever on the Plasma Lipids, Am. J. Dis. Child. **49**:658-671 (March) 1935.

conditions were characterized by narrowed coagulation bands. Widened coagulation bands were obtained by the addition of fatty acids to the serum in vitro. The failure to obtain coagulation bands with the spinal fluids in the present series could be accounted for by the minimal amount of fatty acids present in the spinal fluid.

SUMMARY

The technic of the Weltmann serum coagulation reaction is given in detail.

In syphilis, the tendency toward widened coagulation bands was present in all stages in direct proportion to the duration of the disease. In dermatoses, the bands varied according to the nature of the disease; those of an exudative and acutely inflammatory character caused narrowed bands, and those of a chronic proliferative nature showed widened bands. In some conditions where widened and narrowed bands reflected the pathologic process, other nonspecific tests showed no such reaction.

The mechanism of the Weltmann serum coagulation reaction is discussed. It is suggested that while protein and calcium are essential in the performance of the test, the determining factor in its mechanism is closely linked with the fatty acids by reason of their presence in decreased values in acute inflammatory conditions, their presence in increased values in chronic inflammatory diseases, their role in determining the processes of fibrosis and of calcification in a number of diseases, the increase in range of the coagulation bands by the addition of fatty acids in vitro and the failure to obtain coagulation bands with the spinal fluid.

Dr. Herman Beerman suggested this problem.

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# MONILIAL GRANULOMA

## Report of a Case and Review of the Literature

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MONILIAL granuloma is a rare specific disease entity resulting from Candida albicans infection. It begins in infancy or early childhood, often as simple oral thrush, and ultimately involves three sites: the oral mucosa, the finger nails and paronychial tissues and the skin of the scalp and face. The skin of the trunk and extremities is rarely involved. In contrast to the banal superficial forms of moniliasis, such as thrush, perlèche, erosio interdigitalis blastomycetica and other intertriginous eruptions, monilial granuloma is characterized by an inflammatory reaction extending into the corium and consisting of granulation tissue similar to that in the deep mycoses.

This report is based on observation of 1 case by us, and on reports of 13 cases uncovered in the literature.

### REPORT OF CASE

G. S., a 7 year old white boy, was first seen in February 1948, with the history of "growths" on the skin since the age of 11 months. First, on the vertex of the scalp, a "cradle-cap-like" dry, hard, scaling process was observed, which gradually enlarged peripherally, and became thicker as layers of scales cohered. During the next two years new "sores" appeared on the scalp, forehead, nose and cheeks, and hornlike structures arose from these lesions. The horny growths fell off periodically and were replaced by new growths. Occasionally, pus was seen at the bases of the lesions.

At 1 year the tips of the thumbs and the left index finger were pinched and subsequently became swollen, and the nail plates became severely altered. The nail changes appeared proximally and extended distally until the entire nail bed was altered. The involved nail plates fell off periodically.

At 4 years the teeth had become eroded and broke off easily, and it was then noted that the oral mucosa and tongue were involved with an adherent gray membrane. Later, the lips became swollen, crusted and cracked.

The growth, general health and intelligence of the child were not impaired. Treatment given in the past by several physicians and hospitals was unsuccessful.

The patient had had measles and chickenpox. He had never been outside Chicago and had not been in contact with anyone with a similar eruption.

From the Section of Dermatology, Department of Medicine, University of Chicago (Chief of Service, Dr. Stephen Rothman).

Both parents were living and well. There were four siblings, aged 3, 5, 10 and 15. All were in good health and without any cutaneous diseases. There was no family history of cutaneous disease, diabetes or allergy.

*Physical Examination.*—The patient was a well developed and well nourished boy. He was somewhat hoarse. He had an eruption involving the scalp, forehead, nose, cheeks and lips (fig. 1). The primary lesion was a highly vascularized papule about 5 mm. in diameter, covered with a thick, adherent, yellow-brown crust and surrounded by erythema and edema. The entire nose and more than half of the forehead were covered with plaques which formed by confluence of the papules. Many of the discernible individual papules on the forehead and

Fig. 1.—Patient aged 7 years. Appearance of face and scalp on first admission.

cheeks were surmounted by hornlike structures. These were hard, dark brown, columnar and either homogeneous or lamellated. The diameter varied from 4 to 8 mm. and the length from 1 to 2.5 cm. (fig. 2). If the crusts or horns were stripped off, profusely bleeding granulation tissue appeared at the bases. The bottom side of the crusts showed prominent follicular plugs.

The lesions on the scalp consisted of numerous bizarre horny structures and large areas of erythema and scaling. In between, irregularly shaped atrophic areas were seen, with partial loss of hair and follicular pores. The shorter horns were knoblike; the longer ones curved in lines parallel to the hair. All were penetrated by hairs, which grew out of the distal tip of the horns. Some were hollow at their bases and were attached to the scalp only at the periphery. The hollow portion had a roughly pyramidal shape. The base of the horns was a

friable, easily bleeding granulation tissue which extended in digitations along the hair shafts. Some crusts became detached from their bases but remained adherent to the hairs. The scarring alopecia, together with some deep-seated crusts reminiscent of scutula, suggested favus. However, there were no stumps or broken-off hairs.

The palpebral conjunctivas were swollen and congested and exhibited a few yellow pustules. There were superficial erythema, scaling and crusting within

Fig. 2.—Close-up picture of left side of face, showing multiple horn formation.

both pinnae. There were no lesions on the nasal mucosa. The lips were swollen, crusted and deeply fissured between the crusts (fig. 1), and the mucosa on the inner portion of the lips was thickened. The buccal mucosa, the posterior part of the hard palate and the tongue showed adherent pseudomembranes which bled profusely if scraped. The tongue also displayed some loose desquamated epithelium and deep furrows. The teeth were all carious, many of them practically eroded away, and there were numerous retained roots. The gingivae were inflamed and swollen. There was strong fetor oris. The pharynx proper revealed no abnormalities. Direct and indirect laryngoscopy were attempted, but the patient

refused to cooperate. It is believed that the laryngeal structures were involved because of the patient's hoarseness. The cervical and submandibular nodes were swollen bilaterally.

Fig. 3.—Photomicrograph of a crust showing clusters of spores and segmented hyphae; × 2,200.

Both thumbs and the left index finger showed "drumstick-like" livid, painless swelling of the distal phalanx. The nail plates on these fingers were rough, opaque and irregularly heaped-up into large pyramidal structures.

The remainder of the physical examination was noncontributory. The hair and skin lesions did not fluoresce under filtered ultraviolet rays.

*Laboratory Examinations.*—Routine laboratory tests gave normal or negative results. A glucose tolerance curve was normal. A microfilm of the chest and roentgenograms of the skull and hands showed no abnormalities. An intradermal test with oidiomycin (0.1 cc. of a 1 : 30 dilution) elicited a 4 plus reaction after

Fig. 4.—Spores, hyphae and chlamydospores attached to short curved rods.

twenty-four hours. A skin test with trichophytin (0.1 cc. intradermally) elicited immediate and delayed negative responses.

*Mycology and Bacteriology.*—Scrapings from all sites revealed, in potassium hydroxide preparations, a tremendous number of fine, straight, poorly refractile hyphae, some of which had swollen terminal endings. There were clusters of

small round cells, probably spores (fig. 3), and larger circular bodies with thick walls, obviously chlamydospores, which were attached to short curved hyphae (fig. 4). It was found that the details of the hyphal structure could be better visualized if the crusts were first soaked in mercuric bichloride solution 1:500 for five minutes and then cleared, in the usual way, by treating the material with 10 per cent potassium hydroxide solution and boiling for a few seconds. Figures 3 and 4 are photographs taken of such preparations. The hair, under potassium hydroxide, contained no hyphae, spores or air bubbles.

Cultures on Sabouraud's medium of material from the lesions, stool and saliva yielded growth, after three to five days, of flat, smooth, whitish colonies with a yeasty odor. Some colonies grew only on the surface and had polycyclic borders, with radial striations at the periphery, and an undulating central portion. Other colonies invaded the medium and showed many fine subsurface radial digitations extending beyond and beneath the surface growth. No fungus grew from hair which was cleaned of all crusts.

Culture mounts taken from the surface colonies showed oval or circular budding spores. Mounts of the subsurface growth showed segmented hyphae and clusters of spores about the intersections. Subcultures on corn meal agar showed many chlamydospores in the culture mounts. Slide cultures with these mediums yielded the same findings.

The organism fermented glucose and maltose, with formation of acid and gas, but did not ferment lactose or sucrose. A complement fixation test with the patient's serum and organism was positive in a dilution of 1:100. The patient's serum agglutinated the organism in a dilution of 1:1,000. Normal controls gave negative reactions.

A saline suspension of the organism was injected into the ear vein of a rabbit. The animal died after five days, and at autopsy both kidneys were swollen and studded with abscesses. An abundant growth of the organism was recovered from the abscesses.

Smears taken from the lesions of the nose, lips and mouth revealed a hemolytic Staphylococcus aureus and occasionally hemolytic streptococci. A biopsy specimen from the granulomatous base of a cutaneous horn yielded abundant growth of hemolytic staphylococci and diphtheroids. However, when on one occasion the deeper part of a biopsy specimen was implanted on blood agar and on nutrient broth, the tubes remained sterile. The only organism which could be cultured invariably from all lesions at all times was a fungus which in all respects was indistinguishable from C. albicans. Therefore, it was concluded that the eruption was due to infection by C. albicans with secondary infection by pathogenic bacteria.

*Histologic Examination* (fig. 5).—There were hyperkeratosis and acanthosis. The corium was filled with a dense infiltrate consisting of lymphocytes, plasma cells, polymorphonuclear leukocytes and foreign body giant cells. The infiltrate extended downward to the subcutis and was perifollicular and periglandular in some areas. The walls of the blood vessels were thickened. Fine filaments, which were probably hyphae, were seen in the stratum corneum.

*Clinical Course.*—The patient was hospitalizd for a period of nearly eight months. Therapy was both systemic and local. He was given a high protein, normal fat and low carbohydrate diet. Injections of oidiomycin in increasing strengths were given three times weekly. Vitamin A, 150,000 units daily for twenty days; calciferol (vitamin D), 100,000 units daily for thirty-four days, and saturated solution of potassium iodide up to 20 drops three times a day were also given.

The local therapy was of three principal types: fungistatic, bactericidal and keratolytic. The fungistatic ointments which were tried were as follows: zinc-undecate (desenex®), salinidol® (salicylanilid, 5 per cent; and carbowax,® 95 per cent) Castellani's paint, trimethyl cetyl ammonium pentachlorophenate (TCAP)

Fig. 5.—Photomicrograph of a biopsy specimen taken from the scalp; × 25.

ointment and methylrosaniline chloride in 2 per cent and 10 per cent concentrations. The antibacterial remedies used were ammoniated mercury ointment with and without salicylic acid, 4 per cent urea peroxide in anhydrous glycerin, intraderm sulfur,® and 1 per cent "tyroderm" tyrothricin ointment. The keratolytic ointments contained salicylic acid and pyrogallic acid.

Two roentgen ray treatments of 1/4 skin unit were given to the face with subsequent flare-up of the lesions. The nails were treated with 2 per cent chrysarobin ointment and also with 10 per cent alcoholic solution of methylrosaniline chloride.

The horns could be easily removed by means of keratolytic agents and their reappearance suppressed by mild ointments. However, the majority of the granulations have resisted all treatments. The anterior half of the vertex of the scalp has healed leaving some scarring and partial alopecia. A few lesions on the forehead and on the right cheek have healed, some leaving groups of small pitted scars and others healing without scarring. The mucosal lesions are as extensive now as they were when the patient first came under our care, and a new nail

Fig. 6.—Appearance of face and scalp after eleven months of treatment. Note clearing of anterior part of scalp and portions of the forehead and nose, but, at the same time, spread of lesions on the cheeks.

plate has become infected. In spite of the essentially unsuccessful therapy, the appearance of the face has been improved under treatment, mainly because of removal of the horns and crusts (fig. 6). The findings in potassium hydroxide preparations have remained unchanged, and cultures from all lesions and the feces yield a strong growth of C. albicans in spite of all the therapy.

## SUMMARIZING REVIEW OF THE LITERATURE

After this eruption had been interpreted as being a peculiar form of monilial infection, we searched the literature for similar cases and were able to uncover thirteen case reports strikingly similar to our case in all

respects.[1] In many cases the pictures of the scalp, face and nails nearly duplicated ours.[2] For brevity's sake these cases will not be reviewed individually; however, the data are summarized in order to point out the characteristic features of monilial granuloma.

The age of onset is always in early childhood. In 5 cases the eruption appeared during the first year of life and in the remainder before the fifth year. There is no sexual predisposition. Six of the patients were female, and 7 were male. Twelve patients were white, and 1 was a Negro.[1h]

The primary site of the infection was the oral mucous membrane in 6 cases and the scalp or the face in 5 cases. In 2 cases the original site was not reported. Stereotypically recurring sites of predilection were the face, lips and buccal mucosa (12 cases); thumb nails (13 cases); other finger nails (10 cases), and scalp (9 cases). In addition, lesions were found on the ears and trunk (6 cases); palate (5 cases); neck (4 cases), and eyelids, pharynx and extremities (3 cases). In no cases were the toe nails infected by C. albicans.

The description of the clinical appearance of the lesions of the scalp, glabrous skin, oral mucosa, fingers and nail plates closely resembled

1. (*a*) Forbes, J. G.: A Case of Mycosis of the Tongue and Nails, Brit. J. Dermat. **21**:221 (July) 1909. (*b*) Patzschke, W.: Ueber einen Fall von Parakeratosis scutularis, Arch. f. Dermat. u. Syph. **131**:312, 1921. (*c*) Lombardo: Per la conoscenza della Endomycose cutanea, Riunione d. Soc. ital. Dermat. **17**: 243, 1920; reviewed by Balzer, F.: De l'endomycose cutanée, Ann. de dermat. et syph. **4**:136 (March) 1923. (*d*) Pels, I. R.; Dresel, I., and Salinger, R.: An Unusual Eruption Due to an Organism of the Monilia Group, Arch. Dermat. & Syph. **14**:280 (Sept.) 1926. (*e*) Haxthausen, H.: Hautleiden von einer Moniliaart hervorgerufen, Zentralbl. f. Haut- u. Geschlechtskr. **43**:133, 1933. (*f*) Moeller, P.: Un cas d'infection de monilia, Acta dermat.-venereol. **23**:476, 1942. This case was reported first by Haxthausen 1 *e*. (*g*) Downing, J. G., and Hazard, J. B.: Cutaneous Moniliasis Associated with Oral Thrush, Arch. Dermat. & Syph. **31**:636 (May) 1935. (*h*) Crawford, S.: Moniliasis, ibid. **34**:150 (July) 1936. (*i*) Beintema, K., and Folpmers, J. A.: Mycotoruleasis generalisata, Nederl. tijdschr. v. geneesk. **81**:4755 (Oct. 2) 1937. (*j*) Carol, W. L. L.; Cremer, G.; van Haren, H. B., and Bloemen, J. J.: Ein Fall von Mycotorulosis generalisata, Arch. f. Dermat. u. Syph. **187**:177 (Oct.) 1938. (*k*) Joulia, P., and Le Coulant, P.: Les épidermomycoses généralisées de la seconde enfance par champignons levuriformes, Ann. de dermat. et syph. **10**:545 (July) 1939. (*l*) Andrews, G. C.: Moniliasis: Avitaminosis, Arch. Dermat. & Syph. **50**:139 (Aug.) 1944. (*m*) Ayres, S., Jr.: Generalized Moniliasis and Trichophytosis, ibid. **52**:277 (Oct.) 1945. (*n*) Miller, J. L.: Moniliasis, ibid. **54**:484 (Oct.) 1946.

2. MacKee, G. M., and Cipollaro, A. C.: Skin Diseases in Children, ed. 2, New York, Paul B. Hober, Inc., 1946, p. 57. A picture of a fourteenth case was found in this text under the caption of "Moniliasis." This was one of the most typical cases. However, since no information was available on this patient, this case has not been included in our report.

our description in most cases. However, there were individual differences. The edema was variable; in 1 case [1f] the ears were so swollen that they reminded one of elephantiasis, and in another [1k] the eyelids were nearly swollen shut. The involvement of the lips amounted to only perlèche of the corners of the mouth in half the cases but was as severe as in our patient in the remainder. In 1 case [1b] no lesion of the lips or oral mucosa were reported. Horn formation was present in 6 cases on the scalp or face, and in 1 case [1k] was seen on the extremities also. Only 1 case showed horns as large as those presented by our patient. This case was reported by Patzschke under the diagnosis of "parakeratosis scutularis," a rare entity reported only once previously, by Unna,[3] who coined the name. However, the patient described by Unna showed practically no resemblance to Patzschke's patient or to patients with monilial granuloma. The skin and nail lesions and the histologic changes in Patzschke's patient corresponded to those of monilial granuloma. However, no mucosal lesions were described, and a causative organism was not searched for in that case, although the infectious nature of the disease was postulated on the basis of the histologic changes.

In one case [1l] a diagnosis of favus had been made by several dermatologists before the mycologic studies were completed.

Descriptions of the causative fungus, as seen in potassium hydroxide preparations and cultures, corresponded to our findings, but identification by means of growth on differential mediums and animal inoculations were not carried out by most authors. The organism was called Monilia albicans in 5 reports and by one of the many synonyms in each of the remaining reports. Two observers [1e, k] reported the presence of chlamydospores with short hyphae attached to them in scrapings. In hair, hyphae or spores were not seen on direct examination in any case, but growth of the fungus from cultures of the hair was reported in 2 cases.[1d,l] The latter findings apparently were obtained without special precautions to remove adherent crusts from the hair before inoculation. In 1 case [1m] Trichophyton purpureum, in addition to C. albicans, was recovered in cultures from the scalp and face lesions. Agglutination reactions, complement fixation tests and animal inoculations were not carried out in a sufficient number of cases to allow any conclusions to be drawn.

Biopsies were done in 6 cases. All revealed changes similar to those reported by us. Some observers [4] were successful in finding the fungi in

3. Parakeratosis scutularis, in Unna, P. G.; Morris, M.; Duhring, L. A., and Leloir, H.: Internationaler Atlas von seltener Haut-krankheiten, Hamburg, L. Voss, 1890, vol. 3.

4. Lombardo.[1e] Moeller.[1f] Joulia and Le Coulant.[1k]

the epithelium, and one author [1j] reported spores in the corium. The histologic diagnosis was either "chronic inflammation" or "chronic granulation tissue."

In no case was the infection acquired from or transmitted to other persons in this form. However, two authors observed transfer of the infection in a different form. In 1 case [1j] an "infection" of a nurse is mentioned, while in the other [1k] it is stated that a nurse displayed typical erosio interdigitalis blastomycetica from which C. albicans was recovered.

In general, monilial granuloma as reported in the literature is highly resistant to systemic or local therapy. Improvement of the mucosal lesions was reported by one author,[1k] and successful treatment of an infected nail (by fuming nitric acid) was reported in 1 case.[1n] The cutaneous eruption was not quite so unrelenting, and in 1 case [1a] healed without treatment and in 2 cases [1b, g] healed under mild antiseptic therapy. In the remainder of the cases the eruption was, in the main, refractory to treatment, although healing of small areas with residual pitted scars occurred in many patients.

The prognosis for life seems to be poor. Only 4 patients [5] were observed for a considerable length of time, and all 4 died, at the respective ages of 8, 18, 16 and 15 years.[6] In 3 cases [7] the cause of death was a "pulmonary infection." In 1 case [1g] the pulmonary infection was present about one month before death, and acid-fast bacilli were recovered in the sputum. Two patients [8] died during one of the recurrent acute febrile episodes of a chronic pulmonary infection characterized by cough, sputum and bouts of fever. The nature of these infections was not established. In the other fatal case,[1d] the patient died of a febrile illness with leukopenia and enlarged liver and spleen, which was diagnosed as typhoid. At autopsy, however, the following findings were reported:

> There were multiple masses diffusely scattered throughout both lungs—pinhead to large walnut in size. They were firm, and on section showed yellow necrotic centers. The mediastinal glands were enlarged, and both spleen and liver were large. The large intestines had greatly thickened walls which were lined with thick purulent material.

Unfortunately, no bacteriologic or mycologic examinations of any of the autopsy material were reported, and thus it cannot be stated whether

5. Pels, Dresel and Salinger.[1d] Moeller.[1f] Downing and Hazard.[1g] Joulia and Le Coulant.[1k]

6. The death of the patient reported by Moeller [1f] was reported to us in a personal communication from the author.

7. Moeller.[1f] Downing and Hazard.[1g] Joulia and Le Coulant.[1k]

8. Pels, Dresel and Salinger.[1d] Joulia and Le Coulant.[1k]

any of these cases terminated with pulmonary or systemic moniliasis or that death occurred because of an intercurrent infection.

In addition to the 13 cases discussed here, 4 other cases were reported in which the development of granulomatous lesions was attributed to infection with C. albicans.[9] These 4 cases obviously do not belong to the group described in this paper. All 4 patients were adults; the localization of the lesions was without any pattern, and only 1 patient[9a] had mucous membrane lesions. Clinically, abscess formation was the only constant finding, and scrapings and other tissue materials did not reveal large masses of fungi on direct examination, a feature which is characteristic for monilial granulomas as presented in this paper.

## COMMENT

Banal infections of skin and adjacent mucous membranes with C. albicans in man are characterized by being rather superficial acute inflammatory processes involving only the epidermis and the upper part of the corium or mucosa. This is true not only for thrush, monilial intertrigo and monilial paronychia but also for the generalized type of moniliasis. Local cure of such superficial lesions can be achieved rather easily in most cases, because fungicidal agents readily penetrate them. In sharp contrast to this situation, in monilial granuloma, as previously described, the same organism causes reactions through most of the corium and occasionally invades the subdermis. The granulation process leads in many lesions to destruction of connective tissue and scarring. In this form the monilial infection is essentially intractable.

The difference in tissue reaction to the same organism can be due either to an unusually virulent strain of the organism or to different responsiveness of the host. All available data indicate that the latter situation is prevalent in monilial granuloma.

If the organism is transferred to a person with normal resistance the usual superficial and easily treated type of moniliasis results.[1k] This indicates not only that the organism is identical in the two types but also that in monilial granuloma it is not necessary to assume a particularly virulent strain. This is well substantiated also by the fact that transfer of the infection to normal persons has occurred only exception-

9. (*a*) Rockwood, E. M., and Greenwood, A. M.: Monilial Infection of the Skin: Report of a Fatal Case, Arch. Dermat. & Syph. **29**:574 (April) 1934. (*b*) Carol, W. L. L.: Dermatomycosis profunda s. generalisata, verursacht von Candida Albicans, Acta dermat.-venereol. **21**:70 (Feb.) 1940. (*c*) Danbolt, N.: Deep Cutaneous Moniliasis: A Fatal Case of a Peculiar Type, ibid. **21**:98 (Feb.) 1940. (*d*) Moore, M.: Granulomatous Moniliasis Resembling Blastomycosis (Gilchrist's Disease), Mycopathologia **4**:272, 1948.

ally. In our case the patient has lived in close contact with four siblings without contaminating them.

There is a tremendous proliferation of the organism in the infected sites, as contrasted with the common types of moniliasis, in which it is often difficult to demonstrate the organism in direct preparations. The overwhelming number of filaments is so unusual for a yeast infection that even experienced mycologists looking at the potassium hydroxide preparations would doubt their being C. albicans. Especially confusing is the great elongation of the hyphae which resemble the "dissociation forms"[10] described in strains of the fungus which have grown on Sabouraud's medium for several years. These findings suggest that in cases of monilial granuloma the fungus has found a particulary suitable culture medium.

In general, spontaneous C. albicans infections of the skin do not occur with great ease unless there are promoting factors.[11] The two most effective promoting factors are (1) chronic maceration, e. g., interdigital erosions in bartenders and housewives, and (2) diabetes, e. g., multiple intertriginous moniliasis of obese diabetic women. Thus it seems that C. albicans will infect the skin only if changes occur in the superficial layers of the skin which favor the invasion and multiplication of the micro-organism. The existence of monilial granuloma seems to indicate that a constitutional defect in defense mechanisms offers exaggeratedly favorable conditions. The lack of defense basically changes the clinical picture of the infection.

The nature of the constitutional defect of defense in patients with monilial granuloma has not been clarified so far. No disturbance of carbohydrate metabolism could be demonstrated in our patient, and he did not respond to a diet low in carbohydrates. We had no opportunity to find out whether the persons who suffer from monilial granuloma have a specifically lowered resistance to monilial infections only or to infections in general. The fact that 4 out of 14 patients have died at an early age indicates a generally lowered resistance to infections of these patients. However, since the cause of death has not been clarified, the possibility still remains that they were victims of pulmonary or generalized moniliasis.

From the available observations the conclusion is drawn that invasion by C. albicans of a host with particularly low resistance results

10. George, G. S., and Plunkett, O. A.: Dissociation in Candida Albicans, J. Invest. Dermat. **10**:327 (May) 1948.

11. Artificial inoculation of C. albicans into the skin of normal persons with no promoting factors leads to the development of small benign lesions which heal spontaneously in a few days (Raubitschek, F.: Role of Candida Albicans in the Production of Erosio Interdigitalis and Paronychia, Dermatologica **93**:295, 1946).

in an extremely serious disease which in many respects is analogous to the deep mycoses, particularly blastomycosis and sporotrichosis, which, although systemic diseases, may remain restricted to skin and mucous membranes for many years. Such patients may then succumb either to the mycosis, which has become systemic, or to an intercurrent infection.

SUMMARY

A case of monilial granuloma with multiple horn formation is reported and 13 similar cases from the literature are reviewed.

The development of this rare clinical entity is attributed to a lowered resistance of these patients to the invasion of C. albicans.

Dr. C. W. Emmons, Washington, D. C., and Dr. E. D. DeLamater, Philadelphia, confirmed the mycologic studies on materials from the patient.

# NEVUS SYRINGADENOMATOSUS PAPILLIFERUS

## Report of a Case

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IN 1937, Sachs and Lewis [1] said that ". . . Nevus syringadenomatosus papilliferus . . . appears to be a rare dermatosis when judged by the few cases reported in the United States." They reported 5 cases and could find only 1 case previously reported in the United States. Ormsby and Montgomery,[2] as late as 1948, did not mention additional American cases and used the illustration from Stokes's original report of the first case. Sutton and Sutton [3] cited a case reported by Elliott, of a unilateral nevus on a boy's back, and exhibited a photograph of a case of Ronchese's. This last-mentioned case was of a tumor on the sternum of a woman. This tumor had also undergone squamous cell malignant change, and Ronchese kindly lent his slides of this case to me for study. Incidentally, both Elliott's and Stokes's cases were mentioned in 1921 by Ormsby [4] in his discussion of the pathology of pigmented nevi. Lever,[5] in the course of his general discussion of benign tumors of cutaneous appendages, mentioned that he had observed 6 cases and presented two photomicrographs. He did not give clinical descriptions, apparently because this topic was only one subdivision of his more extensive subject.

Thus I found a total of 14 cases reported from the United States; the case here presented is the fifteenth. The original reports are in the European literature, and complete bibliographies were given by Sachs and Lewis [1] and by Lever.[5] The case here reported is, therefore, of interest because of the rarity of the disease, if not for other reasons. At

From the Department of Dermatology and Syphilology, Tufts College Medical School, J. G. Downing, M.D., Professor.

1. Sachs, W., and Lewis, G. M.: Nevus Syringadenomatosus Papilliferus, Arch. Dermat. & Syph. **36**:1202 (Dec.) 1937.

2. Ormsby, O. S., and Montgomery, H.: Diseases of the Skin, ed. 7, Philadelphia, Lea & Febiger, 1948, pp. 745-746.

3. Sutton, R. L., and Sutton, R. L., Jr.: Diseases of the Skin, ed. 10, St. Louis, C. V. Mosby Company, 1939, pp. 620, 621 and reference on p. 627.

4. Ormsby, O. S.: A Practical Treatise on Diseases of the Skin, ed. 2, Philadelphia, Lea & Febiger, 1921, p. 485.

5. Lever, W. F.: Pathogenesis of Benign Tumors of Cutaneous Appendages, Arch. Dermat. & Syph. **57**:691 (April) 1948.

the first glance in the microscope at the section from the biopsy specimen, I saw that the picture was so strikingly characteristic that I recognized the condition at once from my remembrance of the articles in the literature, particularly from my recollection of the colored reproductions by Percival, Drennan and Dodds [6] and by Lee McCarthy.[7]

The case here presented demonstrates certain noteworthy clinical features, as will be discussed.

*Sex.*—The patient was a woman. Although the number of cases from which to draw conclusions is limited, there seems to be a preponderance of incidence in females. This observation is apparently also true of syringocystadenoma (syringoma), of chronic papular eruption of the axillas and pubis (Fox-Fordyce disease), of hidrocystoma and of hidradenitis suppurativa. It is probably more than mere coincidence that these abnormalities of the merocrine glands, both eccrine and apocrine (but especially the latter), have a sex-linked incidence.

*Anatomic Sites.*—In this patient, the lesions were in the inguinal region. Apparently any area of the skin where sebaceous glands are numerous may be the site, i.e., scalp, nose, back, sternum, lip and axilla. Significantly, these are also common sites for sebaceous nevi.

*Gross Morphologic Picture.*—The tumor in this case was a combination of moist, dull red exuberance combined with shiny, translucent nodules. This picture seems to be common to other cases described. An unusual feature in this case was the hyperkeratosis at certain areas.

## REPORT OF CASE

A married white woman, M. O'C., aged *22*, at home, was referred to me by her family doctor because of a lesion in the left groin, present since birth (fig. 1). During childhood, this had been a light red, slightly raised, asymptomatic structure. In the past seven years, it had slowly become more and more raised above the surface, had gradually increased in size and bled easily if traumatized. In the past two or three years, a "crust" would form on the surface, break off at infrequent intervals and then form again (areas of pronounced hyperkeratosis). During the past few years, the moist secretion which had always been present began to have a bad odor (apocrine secretion? infection?).

Over the left inguinal area, running parallel with the inguinal fold, was a tumor of 8 by 2 cm. It was divided approximately at its middle by a space of normal skin measuring about 2 cm. The tumor was an irregular, lobulated, granulating, moist, dull red mass. The central area of each portion was surmounted by a yellowish brown, keratotic, horny excrescence. The ends of these two portions of the tumor consisted of clusters of translucent, light purplish red nodules, from 1.0 to several millimeters in diameter.

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6. Percival, G. H.; Drennan, A. M., and Dodds, T. C.: Atlas of Histopathology of the Skin, Edinburgh, E. & S. Livingstone, 1947, pp. 367-373 and 298.

7. McCarthy, L.: Histopathology of Skin Diseases, St. Louis, C. V. Mosby Company. 1931, pp. 367-368.

The medial portion was removed by electrosurgery and the edges sutured. A good cosmetic result was obtained, with no evidence of recurrence at the site at the end of four months.

*Histologic Report.*—Microscopic examination of a portion of the tumor which had the horny, keratotic surface (fig. 2) disclosed structural conditions similar to those seen in nevus unius lateris and apparently hitherto not described: hyperkeratosis, parakeratosis, acanthosis, thickening of the granular cell layer and thickening of the dermal papillae. Subjacent to this were seen the typical villus-like projections extending into irregular, dilated spaces. The spaces varied from narrow, crowded and twisted irregular passages to large, wide dilatations becoming more open as the surface was approached. The villus projections were lined with the typical double layer of cylindric and cuboidal cells.

Fig. 1.—Close-up picture of lesion of nevus syringadenomatosus papilliferus, present since birth, in a young married woman. The lesion, in two segments, lay along the left inguinal fold.

A nearby spot of this portion of the nevus (fig. 3) showed a large acinus near the surface. This space was lined almost entirely by the double layer of cells typical of this tumor. This double layer more nearly resembled the active secreting phase of apocrine glands than it did the coils of the glandular portion of eccrine glands, although it differed from both.

The layer of cells which immediately lined the space were large, tall and cylindric; their cytoplasm was pale and finely granular; the nuclei were clear, round or oval and lay in the central portion of the cytoplasm. In those cells which were tallest and most closely crowded together, the nuclei were stretched out long and piriform, with the conical end toward the base of the cell, and occupied a much larger proportion of the cell than normally. Some of these taller cells showed an indistinct shredding of their free surface as though their cytoplasm had been

extended into the space which they lined. Where there were masses of debris (exudate? secretion?) adjacent to such cells, lying in the space fine threads could be seen continuous with these irregularly fringed or shredded tall cells. These cells appeared to be in an active phase. In some cells, the nuclei were more spherical and slightly more compact and lay nearer the base of the cells, which were themselves not as tall as their neighbors; they were probably resting.

Immediately below this layer of tall, cylindric cells was a layer of smaller cuboidal cells; there, the nuclei, occupying most of the cell, left so little cytoplasm

Fig. 2.—Photomicrograph showing unusual reaction of epithelium, with pronounced hyperkeratosis, parakeratosis, acanthosis and thickening of the granular cell layer. Below are seen the villus-like projections extending into the irregular, dilated spaces, lined with a double layer of cylindric and cuboidal cells; × 120.

that it was barely discernible. This cuboidal layer seemed to be more fundamental than the cylindric layer because, wherever there was a change from this standard pattern the variation was toward a double layer of these cuboidal cells. They were probably the precursors.

Supporting the aforementioned double layer was a loosely woven stroma of connective tissue which formed the bed of the entire tumor as well as the supporting structure of the villous projections. Through this coursed many blood vessels of

various diameters, producing an angiomatous appearance in some areas. Most striking was a compact infiltrate of plasma cells, densest near the villous and acinous portion of the tumor and extending down as deep as the coil glands where they were less profusely, but nevertheless abnormally, distributed.

Fig. 3.—This photomicrograph of a portion of the nevus shows a large acinus just below the surface; it is lined with the double layer of cylindric and cuboidal cells. The dense cellular infiltrate of the corium is made up largely of plasma cells. Note the dilated, irregular spaces in the upper right corner, where the villous processes, all also lined with the specialized double layer of cells, project. Deep in the corium are dilated coil glands; the section marked *B* is enlarged in figure 4; × 45.

Deeper in the corium of this same section was seen a large area of dilated coil glands (fig. 4). They showed the typical basement membrane supporting the single layer of flattened, compressed cells. In some sections of dilated coils, the

Fig. 4.—Enlarged view of section marked *B* in figure 3. Dilated coil glands with the basement membrane, *BM,* supporting the single layer of gland cells may be seen; × 1,200.

lining cells still retained their larger proportion of cytoplasm, giving a more normal cuboidal appearance.

Fig. 5.—Low power view of section from small, translucent, purplish red nodule from same tumor. A partition separating two loculi, into each of which project a few villi, all lined with the typical double layer of cells, may be seen. Note the transition of epithelium to the double cell layer at the smaller loculus; × 45.

Fig. 6.—A slightly more enlarged view of a section from same site as figure 5, a few microns away, to show details of the structure of the opening onto the body surface. Note how the epithelium merges with the double cell layer lining the loculus; × 90.

A section from one of the small, translucent, purplish red nodules (fig. 5), showed clearly, at a glance, the relation between the microscopic structure and the gross morphologic picture. Two loculi, separated by a partition and into each of which projected a few villi, lay underneath a slightly flattened, acanthotic epithelium. The walls of the loculi and their projections were lined with the characteristic double layer of cells. Floating free were masses of foamy, disorganized, cellular debris. The subepidermal connective tissue, as well as the connective tissue of the partition, showed an infiltrate of plasma cells and nevus cells. The smaller loculus showed how the epidermis dipped down to form the lining of the opening onto the surface and how the transition from epidermis to double cell layer took place.

Figure 6 shows a section at this same site, a few microns away, which revealed the structure of the communicating opening onto the surface.

## SUMMARY

A case of nevus syringadenomatosus papilliferus in a young woman is described. These tumors are commoner in women and at sites where sebaceous nevi are also prevalent. Histologically this particular case presented a hitherto undescribed reaction of hyperkeratosis, parakeratosis, acanthosis and granulosis similar to the changes of nevus unius lateris. The characteristic of the tumor was a double layer composed of tall, cylindric and short, cuboidal cells which lined spaces and passages and loculi as well as projecting villi. The stroma supporting this double layer was highly vascular and infiltrated with plasma cells. There were massed, dilated coil glands in the cutis. The double layer of cells was like neither the cells lining normal sweat ducts nor those of the coil glands, eccrine or apocrine, and yet, in some respects, it did resemble them. Because these cells retained their exact morphologic characteristics throughout their entire distribution, because they were not invasive, because they showed evidence of secreting part of their cytoplasm into channels leading to the surface, they probably represented a benign hamartoma of modified apocrine gland origin. Therefore, rather than syringadenoma a more accurate description of the condition would be nevus spiradenomatosus papilliferus.

ADDENDUM.—Since this report was submitted for publication, another case report, with an extensive discussion, by Herman Beerman has been published.[8] Beerman stressed the usual absence of hyperkeratosis and parakeratosis, both of which happened to be present in the case here described.

281 Ocean Street.

8. Beerman, H.: Hypertrophic Darier's Disease and Nevus Syringocystadenomatosus Papilliferus: Histopathologic Study, Arch. Dermat. & Syph. **60**:500 (Oct.) 1949.

# ACRODERMATITIS PUSTULOSA PERSTANS

## Report of a Case in a Child

WILBERT SACHS, M.D.
NEW YORK
AND
HANS FIELD, M.D.
BRONX, N. Y.

IN AN article on so-called pustular psoriasis,[1] one of us (W. S.) attempted to show that the disease was not related to psoriasis. As mentioned in a later report,[2] in a series of cases of this disease careful repeated clinical examinations revealed no evidence of psoriasis anywhere on the body. Therefore, it was suggested that the term pustular psoriasis be dropped and acrodermatitis pustulosa perstans be substituted.

In our experience, cases of acrodermatitis pustulosa perstans often are diagnosed, both clinically and microscopically, as dermatophytosis, dermatophytids, mycotic eczema, contact dermatitis, pompholyx, nummular eczema or psoriasis. The features of pustules or vesiculopustules seen in the typical clinical picture may be absent at the time of examination and result in a picture which closely simulates the aforementioned dermatoses.

In our studies of clinical cases which were corroborated by characteristic microscopic changes, we were surprised to find that acrodermatitis pustulosa perstans was not as uncommon as usually thought and taught. This observation was in agreement with the view of several experienced dermatologists with whom we have discussed this entity.

Since we have never observed a case of acrodermatitis pustulosa perstans in a child, we feel that the following case [3] should be reported.

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From the Dermatological Department of the New York Polyclinic Medical School and Hospital, service of Dr. A. C. Cipollaro.

1. Sachs, W., and Scannone, F.: So-Called "Pustular Psoriasis," J. Invest. Dermat. **6**:349 (Dec.) 1945.

2. Sachs, W.; MacKee, G. M., and Rothstein, M. J.: Acrodermatitis Pustulosa Perstans (So-Called Pustular Psoriasis), Arch. Dermat. & Syph. **56**: 766 (Dec.) 1947.

3. Sachs, W.: Acrodermatitis Pustulosa Perstans presented before the New York Dermatological Society, March 22, 1949.

REPORT OF CASE

H. S., a white boy aged 12, had acquired at the age of 2 an eruption of the palms and soles characterized by blisters. There had been a recurrence when the child was 4 years old, at which time he had been treated for a fungous infection of the hands and feet. The eruption had persisted with varying severity but at no time had entirely disappeared. In 1947 there had been an exacerbation on the soles, which had subsided with treatment. At one time, in 1946, the patient had been hospitalized and treated with penicillin for a severe infection secondary to the eruption on the toes and plantar surfaces. Staphylococcus aureus A and Staphylococcus albus B were cultured from purulent lesions.

Examination revealed an erythematous, scaly eruption on the palms, with an occasional vesiculopustule (fig. 1). The feet were free of lesions. No focus

Fig. 1.—Erythematous, scaly eruption of the palms, with a few minute pustules.

of infection was demonstrable on complete physical examination. Patch tests to shoe leather and other suspected substances had negative results. Fungi were not found on several examinations, and all tests for fungus allergy had negative results (hospital note). The Wassermann reaction was negative, and the results of urinalysis showed no abnormality. A test with old tuberculin 1 : 10,000 had negative reactions.

*Histopathologic Picture.*—The epidermis was acanthotic, and the basal cell margin was intact. The granular and horn layers were present. The suprapapillary plates were not thin, and there was no parakeratosis. In the center of the section, there was a large epidermic cavity containing numerous polymorphonuclear leukocytes. This was covered with a crust. Little or no edema was seen about the cavity. In the upper portion of the cutis, the vessels were dilated, and

in the margin below the cavity was a moderate focal and diffuse infiltration of small round cells and wandering connective tissue cells. Some interstitial edema was noted in the subepidermic zone (fig. 2). The diagnosis on microscopic examination was acrodermatitis pustulosa perstans.

## COMMENT

As was stated in an article on acrodermatitis pustulosa perstans,[2] some cases resembling the one reported are cases of pustular bacterids of Andrews and Machacek [4] and do clear up with the removal of a focus of infection. A small number are cases of psoriasis of the palms and soles

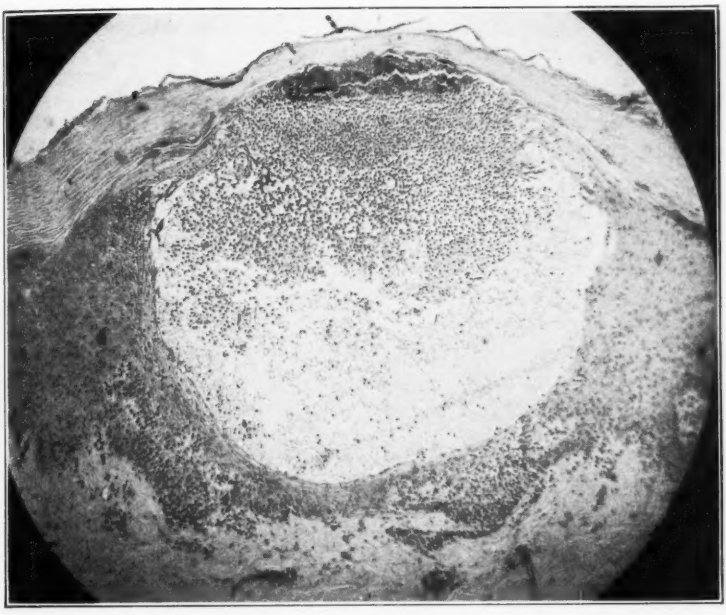

Fig. 2.—Medium power view of large pustule in the epidermis.

with secondary pustules and give the microscopic picture of psoriasis. The majority, we believe, are cases of acrodermatitis pustulosa perstans.

In the case reported there was no history or other evidence of psoriasis and the microscopic picture was not that of psoriasis. The condition was probably not a bacterid, for no focus of infection was found on examination and, during the patient's hospitalization for an acute secondary infection, large doses of penicillin failed to influence

4. Andrews, G., and Machacek, G. F.: Pustular Bacterids of the Hands and Feet, Arch. Dermat. & Syph. **32**:837 (Dec.) 1935.

the primary disease. Thus, the clinical picture, the history and the microscopic changes suggest the diagnosis of acrodermatitis pustulosa perstans.

SUMMARY

A case of acrodermatitis pustulosa perstans in a 12 year old boy, with probable onset at the age of 2, is reported. The disease is not as rare as is usually thought.

6 East Eighty-Fifth Street.

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# Clinical Notes

## TRICHOPTILOSIS DUE TO TRICHOMYCOSIS PALMELLINA PUBIANA (RED)

### Report of a Case

GUILHERME V. CURBAN, M.D.
Assistant, The Dermatologic Clinic, University of São Paulo
SÃO PAULO, BRAZIL

A white male student, 18 years of age, consulted us about alterations, which had been present for two months, in the color and form of the pubic hairs. The patient was concerned, not because of symptoms produced, but because he suspected that the changes possibly were of venereal origin.

On clinical examination, the hairs of the pubic region were found to be thickened and irregularly covered with solid concretions. These concretions, of variable

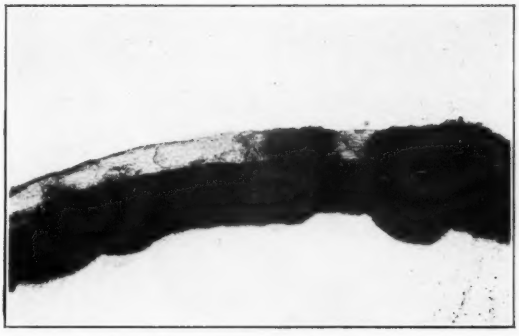

Fig. 1.—Hair of pubis. Note the shaft of the hair in some parts partially involved and in other parts encircled by solid concretions of trichomycosis; × 40 (Zeiss).

dimensions, sometimes totally encircled the shaft of the hairs. They were very adherent and of a lusterless dark red color and could be removed from the hair with great difficulty. Some of the hairs presented an obvious division into two branches, presenting a trichoptilosis that had its initial point in one of these nodular concretions. The adjacent skin was not involved, and the hair of other regions of the body was not similarly involved.

Direct microscopic examination of the hair in a drop of a 30 per cent solution of potassium hydroxide covered with a cover glass showed the shaft of the hair to be involved with numerous red dark nodules that in some areas totally and in others partially encircled it.

Examination of these nodules by the same method, but after dissociation and under the high power lens, revealed, not a homogeneous structure, but a great number of conglomerated, bacillary-like hyphal elements, thin walled and short. Some of them were straight, and others were bent. Beside these hyphal bodies

clumps of cocci could also be observed. No alterations were found in the roots of the affected hairs. All these elements were characteristic of the fungus Nocardia tenuis (Castellani, 1911). Cultures were not made.

Notwithstanding the localization of the infection, the color and structure of the concretions permitted the diagnosis of trichomycosis palmellina of the red variety

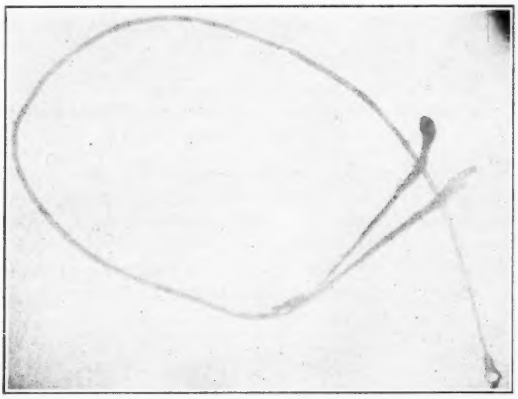

Fig. 2.—Hair of pubis. Note the division of the hair into two branches. The branching has its initial point in one nodular concretion of trichomycosis; × 5 (Zeiss).

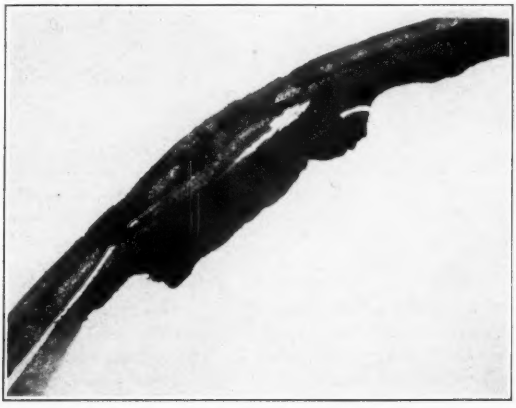

Fig. 3.—Hair of pubis; the same specimen as is shown in figure 2. Detail of the initial point of trichoptilosis, with the nodule of trichomycosis, may be seen; × 40 (Zeiss).

and the exclusion of the one disorder that might be confounded with it, namely, piedra.

The peculiar aspect of this case is represented by the observation not commonly reported, the trichoptilosis directly determined by a parasitic infection of the hair.

Instituto Adolfo Lutz.

# News and Comment

## GENERAL NEWS

**Laboratory Training Courses.**—Laboratory training courses in diagnosis of a variety of infectious diseases will be offered by the Communicable Disease Center, Laboratory Division, Public Health Service, Atlanta, Ga. Courses will be offered from January to December 1950 and will be from one to four weeks long. Information and applications may be obtained from the Chief, Laboratory Division, Communicable Disease Center, 291 Peachtree Street, N. E., Atlanta.

## CORRECTION

In the discussion by Dr. Francis A. Ellis of the article on "Eosinophilic Granulomas of the Skin" by Dr. Edward A. Oliver and others, in the November 1949 issue of the ARCHIVES OF DERMATOLOGY AND SYPHILOLOGY, page 715, the last sentence should read, "The pathologists were unwilling to accept the condition as eosinophilic granuloma but considered the cutaneous lesions to be angioma, apparently an unusual form of Kaposi's sarcoma (multiple hemorrhagic sarcoma), in which there was endothelial proliferation, with large numbers of eosinophils."

# Obituaries

## MAURICE OPPENHEIM, M.D.

**1876–1949**

On Oct. 27, 1949, Maurice Oppenheim, of Chicago, died of coronary disease while asleep. He is survived by his wife Lilly, to whom he was married May 11, 1914, and two daughters, Emmy and Maria.

Oppenheim was born on Jan. 1, 1876, the younger son of an old and very well to do Viennese family. He received his medical training in the School of Medicine of the University of Vienna. In his parental home Oppenheim early in life became acquainted with the arts, particularly with painting. It was due to his early training with the arts that Ehrmann, himself already a distinguished dermatologist and a painter, offered Oppenheim an assistantship at his outpatient clinic. Shortly thereafter I. Neumann appointed Oppenheim assistant in his department. From then on, Oppenheim's progress was rapid. E. Finger, the successor to I. Neumann, made him an assistant professor in 1907 and associate professor in 1917. From 1918 to 1938, Oppenheim headed the department of Dermatology and Syphilology of the Wilhelminen Hospital, Vienna, which in 1928 was rebuilt and reequipped according to his plans and ideas. In 1938 he was compelled to leave Vienna and, after short stays in Paris, London and New York, settled in Chicago, where he was appointed chairman of the Department of Dermatology and Syphilology of the Chicago Medical School. He felt happy in Chicago; he enjoyed teaching and practicing there and often told me how happy he was and that he could not wish for anything better.

Oppenheim was an honorary member of the Minnesota Dermatologic Society, London Dermatologic Society, Austrian Dermatologic Society, Spanish Academy of Dermatology and Syphilology and College of Physicians of Vienna. He was also a corresponding member of the American Dermatologic Association and of the Société française de dermatologie et de syphiligraphie, Argentina asociacion de dermatologia y sifilologia, Dermatologic Society of Berlin, Dansk Dermatologisk Selskab, Société polonaise de dermatologie, Società italiana di dermatologia e sifilologia and Hungarian Dermatologic Society. He had received numerous medals and citations for scientific exhibits. He was an excellent debater and fought hard for his opinions, and, although his aggressiveness was often misunderstood by his opponents, he never meant offense. In 1924 he gave the annual Prosser White Oration to the Fellows of the St. John's Hospital Dermatological Society in London.

MAURICE OPPENHEIM, M.D.
1876-1949

An examination of Oppenheim's scientific contributions, consisting of over three hundred articles and seven books, establishes him as one of the most productive dermatologists of his time. He had a special interest in pigment formation in the skin, the use of roentgen rays in dermatology, the complement fixation test in gonorrhea, blastomycosis, Madura foot, acne conglobata, acetarsone in the treatment of syphilis, dermatoses caused by various acarus mites, onycholysis partialis semilunaris, treatment of scabies, dermatitis bullosa et striata pratensis, dermatotypia in dermatology and acetarsone in the treatment of pemphigus. His main interests, however, were focused on atrophies of the skin (a very comprehensive study of which was published by Oppenheim and Finger in 1910); on necrobiosis lipoidica, the first case of which he presented in 1928 as dermatitis atrophicans et necrotica diabeticorum, and on occupational dermatoses. Numerous were his contributions on cutaneous diseases caused by industry, sports, cosmetics and seasons; his handbook of occupational diseases of the skin (1923-1926, with co-editors Rille and Ullmann) is a lasting source of valuable information; he described many professional stigmas, and his collection of photographs and photochromes of occupational diseases of the skin has gained international repute.

As a teacher Oppenheim was greatly admired and appreciated, not only by his associates but by his students, both undergraduate and postgraduate. While in Vienna he was highly popular with dermatologists from abroad, particularly from the United States and England. There was hardly an annual meeting of the American Medical Association of Vienna or a Thanksgiving Day banquet to which he was not invited. Many lasting friendships were developed between Oppenheim and his students from abroad, many of whom are now among the leading dermatologists of the United States and Great Britain.

Oppenheim was one of the distinguished representatives of the prewar Viennese school of dermatology, and his death will be regretted by dermatologists all over the world. Carlyle said, "The modern majesty consists in work, and what a man can do is his greatest ornament." What Oppenheim achieved is a real ornament, an admirable, impressive contribution to dermatology, and will be remembered as such by many generations to come: "Exegi monumentum aere perennius."

STEPHAN R. BRUNAUER, M.D.

# Society Transactions

## BRONX DERMATOLOGICAL SOCIETY

**Charles Wolf, M.D., *President***

**Henry Silver, M.D., *Secretary***

***March 18, 1948***

**Osteoma Cutis.** Presented by DR. MORRIS LEIDER.

G. S., a white woman aged 34, has been under observation at the Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital for the past seven years. There is a history of acne for the past twenty-one years.

Examination reveals scarring resulting from healed lesions of acne, with little frank activity of acne, considerable traumatic scarring with some fresh excoriations and rosacea-like erythema with telangiectasia. There are no milia present.

The patient submitted about twelve bone-hard concretions which she claimed that she had extracted from the skin of her face in recent months. Microchemical, histopathologic and roentgenologic analysis of these specimens revealed them to be true bone.

The blood calcium content is at the upper limits of normal. There is no evidence of constitutional, and particularly none of endocrine, disease.

DISCUSSION

DR. WILBERT SACHS: I do not think that anyone will dispute that the particles are bone. However, this condition does not correspond to my concept of osteoma cutis. There are several dermatoses in which bone occasionally develops, such as multiple giant cell tumors and scleroderma. This patient has some type of dermatosis in the course of which bone has been formed. Just because bone is formed, the disease is not necessarily an osteoma cutis.

DR. RUDOLF L. BAER: Credit is due to Dr. Leider for having established the diagnosis. This case was presented elsewhere, and, despite evidence of the formation of bone by the skin, some of the discussers were of the opinion that the lesions are calcified cysts. Dr. Leider has brought forth all the additional evidence to clarify this unique clinical picture.

DR. CHARLES F. SIMS: I am of the opinion that Dr. Leider's diagnosis of osteoma cutis is well established.

DR. MORRIS LEIDER: Dr. Sachs's remarks are well taken. However, textbooks refer to two types of extrinsic bone formation, namely, metaplasia and neoplasia. When ossification occurs secondary to a preexisting disease state it is said to be metaplastic; when it arises apparently *de novo* it is termed neoplastic (primary). From a logical point of view, a concept of spontaneity in origin (causelessness) is inadmissable for any medical condition, and therefore the term neoplasia is not to be construed as meaning that. Applied to this case the designation would mean causation such as is vaguely imagined for nevi, fibromas and other benign new growths. On the other hand, one can easily make out a case for metaplastic rather than neoplastic transformation here. Consider twenty-one years of acne accompanied with chronic inflammatory changes and trauma from continuous picking, squeezing and scratching in an area (the face) that is rich in blood vessels and

muscle elements. It can be well imagined that this disorder is myositis ossificans quite comparable to what occurs in equestrians and other persons whose occupation is attended by repeated injury to a particular site.

DR. FRANK E. CROSS: Dr. Leider stressed the psychopathic background of this patient. It is of interest to see an organic condition develop in "pickers."

DR. MORRIS LEIDER: It is well to point out that because a patient exhibits a decided psychopathic habitus one should not instantly dismiss claims and symptoms. This dismissal had been done repeatedly in this case, and I, too, was tempted to act hastily in this manner. I thought at first that the patient was dissembling and presenting artefacts. It is evident from this case that one must check carefully for organic disease even in cases that are most obviously dermatoneuroses.

**Generalized Fixed Eruptions, Eczematization and Hyperpigmentation, Due to Antipyrine Contained in the Cough Remedy 666.®** Presented by DR. JOHN GARB.

**Chronic Lymphatic Leukemia with Leukemia Cutis Nodules and Infiltrated Plaques.** Presented by DR. FRANCES PASCHER.

**Chronic Lymphatic Leukemia with Papular Leukemia.** Presented by DR. FRANCES PASCHER.

**Cholinergic Urticaria and Pruritus.** Presented by DR. RUDOLF L. BAER.

P. M., a white man aged 23, has been studied by Drs. Sidonia T. Furst and James R. Allen at the Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital. About twenty months ago the patient first noticed the onset of an itching erythematous eruption consisting of small white lesions, which followed a severe sunburn contracted a few weeks previously. The attacks are precipitated by heat, exercise and emotional disturbance (such as exposure to hot air or water, sunbathing, boxing, dancing, altercation, laughing and sexual intercourse). Lately the patient has been unable to work because of the severe pruritus. He had considerable relief for a period of three months in 1947 after daily sunbathing, at which time he found quick relief by plunging into the water. The condition again recurred in the fall of 1947 and has persisted to the present date.

The family history reveals that the father has diabetes and a sister has been suffering from "eczema." The patient is a well developed, thin, nervous young man. After exercise a characteristic eruption appears in the following manner: The patient becomes flushed in the face, neck, upper portion of the trunk and, to a lesser extent, on the extremities. Pruritus of the trunk and arms becomes severe and is followed by the appearance of bright red macules 2 to 5 mm. in diameter in the erythematous areas. These macules become red papules, and some of these papules form whitish wheals 3 to 6 mm. in diameter, with a narrow flare of 1 to 2 mm. The attacks subside within fifteen to forty-five minutes. Immersion of an arm or a leg in hot water (46 C.) or injection of pilocarpine or doryl® (carbaminoylcholine) provokes similar attacks within ten to fifteen minutes.

An injection of atropine sulfate (0.0006 Gm.) subcutaneously partially or completely inhibited an attack, while the oral administration of atropine was not beneficial. Pyribenzamine® administered by mouth seemed to inhibit the whealing, without much subjective relief. The patient had partial improvement of the condition for one week after repeated daily immersions of one forearm in hot water

(46 C.). After a severe attack there seems to be a period (twenty-four to forty-eight hours) of relative unresponsiveness, when the eruption is produced with more difficulty and is of a milder nature.

DISCUSSION

DR. SIDONIA T. FURST (by invitation): The clinical picture is well defined and distinguished from common urticaria: Bright flares appear first and are followed by minute wheals in their centers. There is no large spreading of the wheals. There is no whealing on the palms or soles; the hairy parts of the axillas are spared even in severe attacks. The scalp shows only flushing. Duke termed this type "physical" urticaria; it is interesting to note that a mental stimulus can produce a cutaneous lesion. With the greatest regularity an attack was produced by application of heat or by excitement. The same effect was brought about by injections of choline derivatives (doryl®) and pilocarpine.

After an extensive study of this rare type of urticaria Grant and associates arrived at the conclusion that it is neurogenic and provoked through different peripheral nerves. When stimulated by heat, exercise or emotion, these different nerves are probably cholinergic, since the urticaria can be produced by administration of choline derivatives or pilocarpine. Grant and associates stated the assumption that the abnormal reaction lies in the cellular elements of the skin. They respond abnormally to a normal release of acetylcholine. As Dr. Allen has reported, we repeated the most important of the experiments done by Grant and associates and later by Hopkins and Kesten and were able to confirm their results. Antihistaminic drugs, even in large doses, had only a limited effect.

DR. RUDOLF L. BAER: The points which might be stressed are that in cases of this sort, if the theory is correct, one is dealing with hypersensitivity to an autogenous substance. Furthermore, this condition seems to me to be the one dermatosis in which there is considerable evidence that psychic and emotional stimuli can play a major role. In these days when psychosomatic medicine is so fashionable we, as dermatologists, should be extremely careful in the interpretation of psychic factors. Here is a condition in which the psyche can apparently be a major factor in producing an eruption through the medium of acetylcholine. Incidentally, in some of the cases there has been only pruritus, without urticaria. Several such cases attributed to the same mechanism were described in the literature some years ago.

DR. PAUL GROSS: What type of emotion elicits these reactions?

DR. SIDONIA T. FURST: In answer to Dr. Gross, stimuli of emotional or non-emotional nature elicited reactions. For instance, attempts at solution of simple mathematical problems or a discussion of the patient's economic situation were sufficient to bring about a reaction. It was interesting to note that the patient complained of having severe attacks of hives up to the waistline while having sexual intercourse.

**A Case for Diagnosis (Necrobiosis Lipoidica? Granuloma Annulare?); Yellowish Lesions on Elbows and Fingers.** Presented by DR. PAUL GROSS and DR. ELLEN REINER.

DISCUSSION

DR. PAUL GROSS: I never had any doubts about the diagnosis of granuloma annulare in this case. Since there is definite evidence of lipid deposits in the histologic section, one has to assume that the condition which the patient presents

is the result of hypercholesteremia. The necrobiosis of granuloma annulare apparently acts as a locus minoris resistentiae for the formation of lipid deposits. This unique case indicates that in necrobiosis lipoidica the necrosis occurs first, the lipid deposition being secondary.

The therapeutic test with roentgen ray therapy, if successful, may further verify the diagnosis of granuloma annulare.

**A Case for Diagnosis (Parapsoriasis? Poikiloderma? Purpura?); Macular and Petechial Lesions on Lower Half of Trunk and Limbs.** Presented by Dr. HARRY B. FEILER.

**Familial Alopecia Areata.** Presented by DR. ALEXANDER A. FISHER.

**Erythema Palmare et Plantare Hereditarium.** Presented by DR. JOSEPH L. MORSE.

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## LOS ANGELES DERMATOLOGICAL SOCIETY

**Maxwell J. Wolff, M.D., *President***

**Jud R. Scholtz, M.D., *Secretary***

***May 11, 1948***

**Favus of the Scalp.** Presented by DR. N. P. ANDERSON.

**Recurrent Erythema Nodosum (?).** Presented by DR. M. E. OBERMAYER and DR. E. T. FOX (by invitation).

**Aphthous Stomatitis; Possible Periadenitis Mucosa Necrotica Recurrens (Sutton).** Presented by DR. WALTER F. SCHWARTZ, Pasadena, and DR. ROBERT BRUCE (by invitation).

The patient, a 31 year old American white man, was first seen by us on Jan. 5, 1948, complaining of recurrent superficial ulcers of the buccal mucosa and tongue. These ulcers have been present on and off since the patient was 10 years old, last for two to three weeks and then heal without scarring. The patient states he has never been free from lesions for over two weeks at a time. The ulcers have ranged in size from 4 to 6 mm. in diameter. Ulcers have never been present on the genitals or on the skin. At no time since Jan. 5, 1948 has there been any regional lymphadenopathy or fever.

Examination showed several punched-out, well marginated, fairly deep ulcers with necrotic bases. Some of these are moderately indurated, while others appear ulcerated without surrounding tissue reaction. Around the indurated lesions is a zone of erythema. No regional lymphadenopathy is present.

A specimen was taken for biopsy on April 30, 1948. The section showed in the center of the specimen an ulceration of the mucosa. There was spongiosis, downward acanthosis and invasion of the prickle cell layer by numerous polymorphonuclear leukocytes. There was a fairly pronounced and dense infiltration of large and small round cells, extending in some portions through the thickness of the specimen. There was a decided increase in the size and number of the blood vessels in the cutis, with some endothelial thickening.

Treatment has consisted of the oral administration of salicylates, without effect. Vaccination against smallpox has been performed weekly for the past four months, for a total of sixteen vaccinations, without noticeable change in the course of the disease.

DISCUSSION

DR. SAMUEL AYRES JR.: This patient has had a series of vaccinations for smallpox. How was the vaccine administered? We have seen good results in several instances with the use of the intradermal technic where no results have been obtained with the use of the puncture method.

DR. L. E. SAVITT (by invitation): My associates and I have been using a technic devised by Dr. Arnold. That technic consists in dilution of one capillary tube of smallpox vaccine with 0.1 cc. of an isotonic solution of sodium chloride and injecting the resulting solution intradermally at two to four day intervals, the amount sometimes increasing to two and sometimes to three capillary tubes diluted in the same manner.

DR. SAMUEL AYRES JR.: My associates and I have followed 1 patient with an extensive herpes-like eruption who is now apparently cured.

DR. G. HELMS, Long Beach, Calif.: My associates and I have used the intradermal method for years. I have never run a controlled series, but observation of both forms of therapy leads me to believe that the intradermal method is superior to the prick method.

DR. A. F. HALL, Santa Monica, Calif.: So far this discussion has been limited to the technic of giving vaccine; I should like to hear some discussion on the diagnosis. I favor the diagnosis of herpetic aphthous ulcers, particularly in view of the history which stated that at no time does the patient feel any lump or palpable lesion in the mucous membrane, but the first thing that he notices is tenderness or stinging, which is followed by redness, which develops into a "white spot" (early vesiculation?). I should suggest that an attempt be made to isolate the herpes simplex virus in this case; the attempt should be made at the appearance of the "white spot" and before ulceration begins. I agree with Dr. Ayres about the technic of administration of the vaccine. I have been doing it that way for eight or ten years and thought that everyone did it that way.

DR. A. K. JENSEN: Herpetic lesions on the lip many times are ushered in by the exposure to the sun or some trauma. I believe, though, that this person's diet should be investigated. I feel sure that there are certain articles of food that will bring on this type of lesion. I should suggest the use of Rowe's elimination diet. Sometimes the use of dilute hydrochloric acid administered by mouth is beneficial.

DR. M. COUPERUS: I should like to add one more therapeutic suggestion. I have had 2 patients recently with recurrent large aphthous ulcers who failed to respond to any of the measures which have been suggested for the patient under discussion, but who responded to daily doses of 3 Gm. of paraaminobenzoic acid. This therapy may be worth a trial.

DR. MARION B. SULZBERGER, New York: I find that these cases have been quite unsatisfactory in management whether they are actually of recurrent herpes or of recurrent aphthous stomatitis from some other cause. I am glad to hear about this method of vaccination. We have not used it in New York. With repeated ordinary vaccination, there has not been a favorable response in most cases. I think in cases of this kind I should eliminate some of the common offenders from the diet. I think certain articles of diet, such as shellfish, caviar, fruits and chocolate, bring on attacks sometimes. I am very glad to hear about paraaminobenzoic acid. But how do you administer such large doses of it?

DR. LOUIS H. WINER: In 0.5 Gm. tablets.

DR. WALTER SCHWARTZ, Pasadena, Calif.: From what one can learn from reading about Sutton's disease, there are a few salient features which are lacking

in this case, namely, the absence of fever, the lack of definite nodulation preceding the ulcers and the lack of regional lymphadenitis. I believe, however, the history is quite consistent for Sutton's disease. After the extensive discussion this evening, and after having given this case much thought, I feel quite strongly that here again we are dealing with a simple case of chronic aphthous stomatitis.

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## NEW ENGLAND DERMATOLOGICAL SOCIETY

**Francis M. Thurmon, M.D., *President***

**G. Marshall Crawford, M.D., *Secretary***

***April 14, 1948***

**Multiple Dermatofibroma (Histiocytoma) of Face.** Presented by DR. PAUL J. CATINELLA, Boston.

S. R., 58 years old, presents lesions on his face, of twenty years' duration. These small, hard, nontender tumors have been appearing gradually and are entirely asymptomatic.

The lesions are rather well scattered over the anterior aspect of the face. There is distinct grouping over the center of the forehead, where the majority of lesions appear. These are fairly uniform-sized, flesh-colored tumors averaging 4 to 5 mm. in diameter. They are firm, nontender, domed, flesh-colored tumors, with slight translucence, and present a somewhat cystic appearance.

Histopathologic examination of a biopsy specimen revealed circumscribed collections of fibroblasts with many foam cells. No treatment has been administered.

DISCUSSION

DR. FRANCIS P. MCCARTHY, Boston: The terminology of sclerosing angioma suggests a primary hemangioma that undergoes sclerosis. Ultimately it undergoes involution somewhat and becomes a fibrous lesion. If I examined this specimen microscopically from the standpoint of a general pathologist, I should not call the condition a sclerosing hemangioma. Many pathologists use different terminology for the same lesion. Histiocytoma seems to be a more definite and descriptive diagnosis than sclerosing hemangioma. Clinically the lesions are firm and do not suggest blood vessels as such. They are hard right from the beginning, and the microscopic picture does not conform to what the average general pathologist would call a sclerosing hemangioma.

DR. JACOB H. SWARTZ, Boston: I should like to ask the presenter whether he would associate the comedos and the glistening sebaceous adenoma type lesions with the clinical diagnosis. This man may have two diseases.

DR. PAUL J. CATINELLA, Boston: The case was presented because of the interesting pathologic findings as compared with what one sees clinically. There were biopsy specimens from three lesions, and all presented the same picture. Multiple biopsies were done to rule out what Dr. Swartz suggested, that we were dealing with two or three different conditions and that the first biopsy happened to be a coincidental finding. So far as the diagnosis goes, it is a matter of terminology. The section shows circumscribed fibroblasts with varying numbers of vacuolated histiocytes, or so-called foam cells; the number of these cells varies in different sections. In some clinics the term dermatofibroma is used to describe all similar

lesions; in others, if the fibrous tissue contains foam cells the word histiocytoma is used. The term sclerosing hemangioma is also used by many pathologists. In my opinion this varied terminology denotes essentially the same condition.

**Scleroderma, Localized to Right Sole (*En Coup de Sabre*).** Presented by DR. GEORGE E. MORRIS, Boston.

**Sarcoidosis of Skin.** Presented by DR. BERNARD APPEL, Lynn, Mass.

**Chronic Pemphigus of Mouth and Vagina.** Presented by DR. PAUL J. CATINELLA, Boston.

**Tuberculosis Colliquativa.** Presented by DR. G. MARSHALL CRAWFORD, Brookline, Mass.

**A Case for Diagnosis (Dermatitis Herpetiformis or Neurotic Excoriations with Trichocryptomania?).** Presented by DR. ROBERT H. GOLDFARB, Boston.

**Dermatitis Venenata Due to Methyl Orange Dye.** Presented by DR. WALTER F. LEVER and DR. RALPH LUIKART II, Boston.

M. H., a 30 year old white housewife, presents a subsiding eruption of the upper extremities and the anterior aspect of both thighs. The history contained four episodes: 1. A severe contact dermatitis of the hands with a generalized sensitization reaction in 1944 was thought possibly due to substances encountered when the patient was employed in a shoe factory. 2. Another violent episode of dermatitis which appeared on the legs in 1946 and was followed by an exfoliative dermatitis was attributed to sensitivity to dyes in nylon hosiery. 3. In 1947 a severe contact dermatitis affected the perineal region after the application of benzalkonium chloride (zephiran® chloride) solution and was followed by a generalized sensitization reaction (a positive reaction was later obtained to patch testing with the dye employed to tint the benzalkonium solution). 4. The current episode began with an acute contact dermatitis of the arms two months ago and was followed by a mild generalized sensitization reaction. A positive reaction was obtained to patch testing with the brown crepe sleeve lining of a coat which she wore for the first time the night prior to onset of the dermatitis of the arm. The eruption had been slowly clearing with hospitalization and no treatment other than boric acid compresses.

As seen today, this woman's arms and forearms reveal merely a fading erythema with a moderate degree of scaling. The anterior aspects of the thighs exhibit residual evidence of positive reactions to patch tests, which are still distinct squares of light erythema with some scaling.

The nature of this patient's sensitization had been studied with patch tests. She had been found to have strong positive reactions to patch tests with aniline, paraphenylenediamine, paraaminobenzoic acid, paraaminophenol, paraaminophenol hydrochloride, ethyl aminobenzoate (benzocaine), procaine hydrochloride, sudan III, benzalkonium dye and methyl orange in alkaline solution. She had shown completely negative reactions to patch tests with benzol, benzoic acid, benzyl alcohol, acetanilid, benzalkonium, sulfanilamide, sulfathiazole, salicylic acid, orthoform (new), and methyl orange in acid solution. The positive reactions to patch tests with paraaminobenzoic acid had been obtained on three separate occasions. The patient was subsequently given 20 mg. of paraaminobenzoic acid by mouth and manifested pronounced pruritus of the palms and soles within two hours. The

next day she received 100 mg. of paraaminobenzoic acid by mouth and responded again with pruritus of the palms and soles within two hours; then after twenty-four hours erythema and vesiculation developed on these areas, in addition to a blotchy erythema on the arms and forearms as well as erythema, scaling and slight oozing of the ears and periauricular regions. The patient appeared to have a wide but chemically specific epidermal hypersensitivity.

**Dermatitis Venenata Due to Paraphenylenediamine (or Chemically Related Material).** Presented by DR. WALTER F. LEVER and DR. RALPH H. LUIKART II, Boston.

A. S., a 40 year old housewife, presents an eruption on the hands of two months' duration and involvement of the feet which began during the past month. The backs of her hands broke out after the wearing of black gloves over a period of one month. Several weeks later the dorsal aspect of her feet erupted after she had been wearing a pair of dark nylon hose for several days. There is also a history of dermatitis on the arms, neck and axillas ten years ago, which was attributed to a black dress. In each of these three instances there had been a positive reaction to patch testing with the suspected garment.

When first seen about a month ago this patient revealed an acute erythematovesicular dermatitis on the dorsal aspects of the hands and feet. Treatment consisted merely of boric acid soaks, and there was gradual improvement. As seen at the time of presentation there is only a fading erythema with barely perceptible scaling. On the anterior aspect of the left arm is a square of fading discoloration at the site of a positive reaction to a patch test with the dark nylon hose.

This patient had been found to have strongly positive reactions to patch testing with paraphenylenediamine and paraaminophenol. There had been completely negative reactions to patch tests with aniline, acetanilid, benzoic acid, metycaine, salicylic acid, paraaminobenzoic acid, ethyl aminobenzoate, procaine hydrochloride, sulfanilamide, sulfathiazole, orthoform (new), sudan III and methyl orange. She is presented because of her very narrow or limited chemical sensitivity in contrast to that seen in the preceding case.

DISCUSSION OF THE TWO PRECEDING CASES

DR. MAURICE J. STRAUSS, New Haven, Conn.: These 2 cases interested me greatly because they paralleled closely those in the report made about two years ago by Rothman and his co-workers in which they showed the importance of the spatial molecular arrangement in determining whether or not there will be cross sensitivity to related chemicals (Rothman, S.; Orland, F. J., and Flesch, P.: *J. Invest. Dermat.* **6**:191 [June] 1945). In the 2 cases they reported it was possible for them to predict accurately which local anesthetics would produce positive reactions to patch tests, by consideration of the molecular arrangement of the test substances. In discussing that paper, Sulzberger suggested that there might be patients whose sensitivity did not depend on the chemical formula. I was able to demonstrate that he was correct when I encountered 2 patients who were sensitive to tetracaine (pontocaine®). On testing with many local anesthetics, 1 of my patients showed cross sensitivity exactly like that of Rothman's patient and the other exhibited sensitivity to another local anesthetic not chemically related to tetracaine (Strauss, M. J.: *J. Invest. Dermat.* **8**:403 [June] 1947). The 2 patients presented today demonstrate this possibility equally well. In 1 the positive reactions go hand in hand with certain factors in the molecular structure of the test substances; in the other there seems to be no rhyme or reason to the reactions. There are both strange positive reactions and strange negative ones.

DR. RALPH LUIKART II, Boston: Several items deserve emphasis regarding these cases. It was a surprise to learn that the first patient had a negative reaction to methyl orange in a solution with acid $p_H$, but a positive reaction in one with alkaline $p_H$. This tempts one to speculate on the distribution of such a dermatitis in relation to the variations in $p_H$ of the surface of the skin. Ortho or meta substitution in the ring appears to eliminate sensitivity in the first case, and the nitrogen bound to the benzene ring would seem to be essential. The wide collateral but chemically specific sensitivity of the first patient should be contrasted to the narrow or highly limited sensitivity of the second patient since they are both sensitive to paraphenylenediamine. Dr. Rothman and his colleagues found wide collateral chemical sensitivities in two procaine-sensitive dentists, but the sensitivities of the two were chemically identical. The cutaneous phenomenon occurring on oral administration of paraaminobenzoic acid seems worthy of note. The study does not warrant conclusions at this point.

DR. WALTER F. LEVER, Boston: A most interesting feature in these cases is that sensitivity to paraaminobenzoic acid, as far as I know, has not been reported in the literature.

DR. G. MARSHALL CRAWFORD, Brookline, Mass.: Epidermal sensitization to paraaminobenzoic acid has been reported (Sulzberger, M. B.; Kanof, A.; Baer, R. L., and Lowenberg, C.: *J. Allergy* **18**:92 [March] 1947). It was encountered in a study of sensitization by topical applications of sulfonamide compounds; positive reactions to patch tests with related substances, including paraaminobenzoic acid, were found. This substance occurs normally in the human body. Sensitization to paraaminobenzoic acid could thus be expected to induce chronicity of eruptions originally caused by other agents such as dyes, sulfonamide drugs and local anesthetics.

**Mycosis Fungoides.** Presented by DR. PAUL J. CATINELLA, Boston.

**A Case for Diagnosis (Essential Telangiectasia, Possibly Due to Avitaminosis?).** Presented by DR. JOHN G. DOWNING, Boston.

**Hereditary Hemorrhagic Telangiectasia.** Presented by DR. BERNARD APPEL, Lynn, Mass.

**Hemangioma of Face.** Presented by DR. GEORGE E. MORRIS, Boston.

**Lichen Nitidus.** Presented by DR. H. BERTRAM ULLIAN, Everett, Mass.

**Dermatitis Venenata in a Nurse, Due to Streptomycin.** Presented by DR. BERNARD APPEL, Lynn, Mass.

**A Case for Diagnosis (Nodular Nonsuppurative Panniculitis or Leprosy?).** Presented by DR. PAUL J. CATINELLA, Boston.

**Erythroderma Ichthyosiforme Congenitum.** Presented by DR. FRANCESCO RONCHESE, Providence, R. I., and DR. BENCEL L. SCHIFF, Pawtucket, R. I.

**Cheilitis Exfoliativa.** Presented by DR. JOHN ADAMS JR., Boston.

**Nevus Pigmentosus.** Presented by DR. GEORGE SCHWARTZ, Malden, Mass.

**A Case for Diagnosis (Pityriasis Lichenoides et Varioliformis or Parapsoriases en Plaque?).** Presented by DR. BERNARD APPEL, Lynn, Mass.

**A Case for Diagnosis (Dermatitis Due to Undetermined Cause? Occupational Dermatosis?).** Presented by DR. FRANCESCO RONCHESE, Providence, R. I.

S. E., a 61 year old white laborer of Italian ancestry, presents a chronic dermatitis of the neck, arms, groins, buttocks and popliteal spaces, of about eighteen months' duration. The patient stated that his first difficulty developed on the hands and arms after he had unloaded oil barrels from a railroad car. This eruption became rapidly generalized and went through an exfoliative phase. He was hospitalized on three occasions between November 1946 and June 1947. The exfoliative dermatitis gradually subsided, leaving the present chronic eruption. In spite of its widespread extent and chronicity there has been comparatively little itching or other discomfort. The patient denied any previous cutaneous disorder, and his general health has been good.

Examination at the time of presentation reveals a generalized brownish discoloration of the skin, with scattered irregular areas of depigmentation. The neck, arms, inguinal regions, genitalia, buttocks and popliteal spaces exhibit well delimited lichenification, which is so thick in some portions as to have an almost verrucous appearance. The finger nails and toe nails show irregular discolorations of assorted hues, and there is some lysis at the lateral and free edges of the nails (fig.).

Examinations of the blood and urine gave repeatedly normal values. A biopsy specimen was obtained in December 1947 from the extensor surface of one elbow, and the histopathologic changes were reported as follows: "The dermis showed pronounced chronic inflammatory reaction. The blood vessels were congested, and there was proliferation of the newly formed capillaries and of fibrous tissue. There was dense and diffuse infiltration of lymphocytes, plasma cells and eosinophils. The diagnosis was chronic dermatitis."

The patient has been treated with ultraviolet irradiation, autohemotherapy, administration of BAL (2,3-dimercaptopropanol), four transfusions of 200 cc. of whole blood, amino acids given by mouth and administration of thiamine hydrochloride, estradiol benzoate (progynon B®) and a multitude of topical applications. Roentgen therapy was administered in a dose of 70 r per area, with six exposures each. The generalized exfoliative dermatitis gradually subsided, but the present areas of lichenification have remained unchanged for the past ten months.

DISCUSSION

DR. BERNARD APPEL, Lynn, Mass.: One feature of this case struck me rather forcibly, namely, the peculiar reticulated pigmentation of the neck, particularly along the sides and over the clavicles. Only the presence of a sharply outlined lichenified plaque in the center is against the diagnosis of poikiloderma of Civatte or perhaps the type described by Riehl. The lesions about the mouth and particularly at the oral commissures might be related to riboflavin deficiency.

DR. JOHN G. DOWNING, Boston: I should like to call attention to lesions on the nasal mucous membrane, on the septum and in the mouth. There are angular, flat papules on the scapular areas which have a violaceous color. I should make a diagnosis of lichen planus. I have a patient now with the same type of pronounced lichenification of the inguinal folds, patches of hypertrophic lichen planus on the inner and outer aspects of the legs and the same type of leukoplakic lesions of the mucous membrane. A biopsy specimen should be obtained from the scapular region.

Verrucous lichenification in patches on skin and mucous membrane, with pachyonychia; sequelae of an exfoliative generalized dermatitis of undetermined origin.

DR. FRANCIS P. MCCARTHY, Boston: The lesions along the lines of occlusion on the buccal mucous membrane and at the oral commissures are at the classic locations for leukoplakia. The patient smokes four Italian cigars, corresponding to eight ordinary cigars, a day. There is also evidence of trauma along the lines of occlusion as well as in a localized area in the left molar region, where the patient has a saber-sharp tooth cutting into the hyperkeratotic mucosa. These changes suggest a verrucous type of leukoplakia. I agree with Dr. Downing that the condition could be lichen planus, but I have not seen that disease produce such hypertrophy in the oral cavity. A biopsy specimen from the buccal mucous membrane lesions would be helpful in determining whether this disorder is verrucous leukoplakia or hypertrophic lichen planus.

DR. FRANCESCO RONCHESE, Providence, R. I.: A biopsy will be performed. I think the lesions in the mouth are areas of mucous membrane lichenification, analogous to those on the skin.

DR. FRANCIS P. MCCARTHY, Boston: What would you call these lesions in the oral cavity?

DR. FRANCESCO RONCHESE, Providence, R. I.: I should call them sequelae of an exfoliative stomatitis.

FOLLOW-UP NOTE (November 1949).—Specimens for biopsy were taken from a verrucous area on the lower portion of the abdomen and from the mucous membrane of the mouth on April 27, 1948. Observations were reported as consistent with lichen planus.

By the end of July 1948 all the verrucous areas became perfectly smooth like normal skin, but with pronounced depigmentation. They maintain at the present time a vitiligo-like appearance. The patient appears to be in good health.

**Multiple Idiopathic Hemorrhagic Sarcoma.** Presented by DR. PAUL J. CATINELLA, Boston.

**A Case for Diagnosis (Urticaria Pigmentosa or Verruca Plana Juvenilis?).** Presented by DR. GEORGE SCHWARTZ, Malden, Mass.

**Tuberculosis Papulonecrotica with Tuberculous Keratitis.** Presented by DR. BERNARD APPEL, Lynn, Mass.

**A Case for Diagnosis (Cellulitis of Loin or Erysipeloid Carcinoma?).** Presented by DR. WILLIAM J. MACDONALD, Boston.

**Herpes Simplex with Generalized Lesions.** Presented by DR. JOHN G. DOWNING, Boston.

J. A., a 4 year old white girl, presents an eruption of five days' duration. A week previously this child had an infection of the upper respiratory tract and for three days sustained a temperature of 100 F. Five days before presentation a cluster of vesicular lesions appeared on the left thigh. That night similar lesions were noted on her face, and the next day others were found about the anus. These vesicles presented an erythematous ring when first seen and were distinctly painful. At the time of presentation they are undergoing involution.

This little girl has clustered, partially dried vesicles on the right cheek, right lower eyelid, medial portion of the left thigh and about the anus. Those on the face and thigh are more extensive, consisting of multiple clusters, and many of

them are already dried, with adherent crusts. The vesicles in the perianal region still exhibit an erythematous base; some of these have been ruptured and appear to be small red dots covered with macerated epithelium. There is also a mild degree of secondary infection in this region, evidenced by a few pustules.

No laboratory procedures or treatment has been carried out.

DISCUSSION

DR. WILLIAM B. SWARTS, Greenwich, Conn.: This patient may have vaccinia from an accidental vaccination; all the lesions seem to be at about the same stage.

DR. MAURICE M. TOLMAN, Boston: This is most interesting and unusual. How often has generalized herpes simplex of this type been seen? What are the chances of recurrence? What about susceptibility to similar virus diseases?

DR. JOHN G. DOWNING, Boston: I presented this case because of the extensive and bilateral distribution of patches of grouped vesicles. There was no history of vaccination; the condition does not resemble an eczema vaccinatum, which is usually acute with a febrile course and goes through typical stages. The lesions of vaccinia are not grouped, as are those characteristic of herpes simplex. As early as 1904 Tyzzer (*J. Med. Research* **11**:180, 1904) described what he believed to be the etiologic factor in vaccinia, when he demonstrated that the rabbit's cornea after inoculation showed the presence of small bodies in the cytoplasm of the epithelial cells. According to Riley and Callaway (*J. Invest. Dermat.* **9**:321 [Dec.] 1947), in eczema vaccinatum the reaction to Paul's test is negative and Guarnieri and Paschen bodies are found in the cornea of a rabbit after inoculation. Inoculation of a rabbit's cornea with the virus of herpes simplex causes severe keratoconjunctivitis and meningoencephalitis.

DR. GEORGE E. MORRIS, Boston: This girl has pediculosis capitis. That can account for much of the secondary infection.

**Tuberculosis Verrucosa Cutis.** Presented by DR. S. J. MESSINA, Boston.

**A Case for Diagnosis (Atrophoderma Maculatum, or Ulerythema?).** Presented by DR. AUSTIN W. CHEEVER, Boston.

**A Case for Diagnosis (Sarcoidosis of Skin or Lupus Erythematosus?).** Presented by DR. GEORGE SCHWARTZ, Malden, Mass.

**A Case for Diagnosis (Lichen Planus Hypertrophicus, Neurodermatitis Circumscripta or Localized Amyloidosis of Skin?).** Presented by DR. WILLIAM R. HILL JR., Boston.

**A Case for Diagnosis (Tuberculosis Verrucosa Cutis?).** Presented by DR. BERNARD APPEL, Lynn, Mass.

**Dermatomyositis.** Presented by DR. GEORGE E. MORRIS, Boston.

**A Case for Diagnosis (Lupus Erythematosus or Lichen Planus with Vesicular Lesions?).** Presented by DR. GEORGE SCHWARTZ, Malden, Mass.

**Localized Myxedema of Skin in Thyrotoxicosis.** Presented by DR. S. J. MESSINA, Boston.

## NEW YORK DERMATOLOGICAL SOCIETY

**George M. Lewis, M. D., *President***

**John C. Graham, M.D., *Secretary***

***Feb. 24, 1948***

### IN SPECIAL HONOR OF DR. HOWARD FOX

**Mycosis Fungoides.** Presented by DR. CHARLES S. LINCOLN JR. for DR. GEORGE C. ANDREWS.

A. R., a man aged 51, is presented from Vanderbilt Clinic with a generalized eruption of seven years' duration. In 1941 a pruritic eruption developed on the arms. The patient's family physician made the diagnosis of "ringworm" and treated him with benzoic and salicylic acid ointment (Whitfield's ointment). The patient's health had always been good. He had had a mildly pruritic eruption involving the groins in 1932 and again in 1934, which had cleared rapidly on both occasions after application of a salve.

In 1942 he consulted a dermatologist who from histologic examination made the diagnosis of mycosis fungoides. The patient was treated with generalized ultraviolet irradiation and topical remedies until March 1944, when he was referred to Dr. Andrews for roentgen ray therapy. At that time he had a generalized, fairly symmetric eruption consisting of variously shaped, flat or slightly raised, sharply limited, red, slightly scaly lesions. The borders at times were polycyclic and slightly raised. A few lesions contained pea-sized tumors. The areas most affected were the neck, shoulders, back, axillas, hips, buttocks, thighs and popliteal spaces. There was no lymphadenopathy.

From March 1944 until January 1948 the patient was treated with fractional doses of roentgen rays at weekly intervals. There was temporary regression of the lesions following each treatment, and there is still satisfactory response to this therapy. Besides many topical remedies he received chaulmoogra oil and estradiol (progynon®) and testosterone parenterally administered, with little change in the eruption. In May 1947 the patient went to Peru and was without treatment for nearly a month. On his return the eruption had become much worse. He was given 5 cc. of a 1 per cent solution of tartar emetic intravenously at weekly intervals, with a pronounced initial response. Without any other treatment, there was a resolution of many lesions, especially on the arms. However, he complained of progressive weakness, vertigo and desire to sleep. After eleven injections he was so weak that he could not go to the office for treatment.

On Jan. 21, 1948, the patient was admitted to Presbyterian Hospital. He was given teropterin® (sodium pteroyl triglutamate) intramuscularly at the rate of 10 mg. daily for one week and 20 mg. daily thereafter for three weeks. There has been no change that can be attributed to sodium pteroyl triglutamate. In conjunction with this treatment, fractional roentgen ray exposures have been given at weekly intervals, with improvement of the lesions irradiated. On February 4 the left thigh was painted with 5 cc. of thorium X solution (1,000 electrostatic units per cubic centimeter). The following week the left leg was similarly treated and the left thigh was repainted with 5 cc. of thorium X solution, containing 2,000 electrostatic units per cubic centimeter. This procedure was repeated on February 18.

At the time of presentation the patient shows a widespread, fairly symmetric eruption consisting of bizarre-shaped, red, sharply demarcated and infiltrated lesions. The infiltration is especially pronounced at the borders of the lesions. Some lesions show only moderate crusting and scaling, and others are moist,

open sores. The fungating lesions which on admission were noted on the occipital region of the scalp, the left side of the neck, the trunk, the buttocks and the backs of the thighs, have flattened and now present either thick crusts or slightly elevated, raw, oozing areas varying from that of a dime to that of a half dollar in size. There is no adenopathy.

The Wassermann reaction of the blood was negative. In the iodine tracer test 40 microcuries of radioactive iodine was given intravenously. The twenty-four hour uptake was 23 per cent (normal, 15 to 30 per cent).

Repeated blood counts have revealed a leukocyte count ranging between 9,000 and 19,000. The most recent showed 16 Gm. of hemoglobin, 5,500,000 red blood cells, and 17,000 white blood cells, with 69 polymorphonuclear leukocytes, 21 lymphocytes, 3 monocytes, 6 eosinophils and 1 basophil.

Biopsy showed a poorly demarcated, irregular epidermis which was flattened in some areas and acanthotic in others. Irregular areas of slight hyperkeratosis and parakeratosis were also seen. The epidermis and upper portion of the corium were massively infiltrated with a variety of types of cells, and many micro-abscesses were visible in the epidermis. These were for the most part filled with large and small cells of the lymphocytic series. Elsewhere the infiltrate found in the upper part of the cutis and epidermis was made up mainly of cells with large vesicular nuclei and small lymphocytic cells. Many of the larger cells showed mitotic figures. A few plasma cells and eosinophils also appeared in the infiltrate, but polymorphonuclear leukocytes were almost entirely lacking. In this area there was some increase in the reticulum fibers but little or no tendency toward the clumping of reticulum cells. The middle and deeper portions of the cutis were also widely infiltrated with the types of cells previously described, but eosinophils, plasma cells and polymorphonuclear leukocytes were relatively more numerous. The entire picture was that of mycosis fungoides, but one cannot rule out lymphosarcoma, and an eventual clinical picture of that disease in this case would not be surprising. The diagnosis was mycosis fungoides.

DISCUSSION

DR. DONALD M. PILLSBURY, Philadelphia (by invitation): I should like to inquire whether when patients are intolerant to antimony potassium tartrate other forms of antimony, such as stibophen (fuadin®), are effective. I presume that the use of nitrogen mustard is being considered in this case, though my associates' and my limited experience would certainly indicate that the favorable effect of that agent in most cases is temporary and that some patients are, within a short time, worse off than they were before nitrogen mustard therapy was started.

DR. EARL D. OSBORNE, Buffalo (by invitation): My associates and I have treated quite a few patients with mycosis fungoides with nitrogen mustard. We were particularly interested in whether this treatment would render the disease more susceptible to roentgen treatment than it had been prior to the use of nitrogen mustard. This effect resulted in 1 case only, and was temporary. The condition rapidly regressed, and the patient died of his disease within six months after receiving treatment with nitrogen mustard. I agree with Dr. Pillsbury that results have been temporary and the disease has progressed in the usual manner. I feel that nitrogen mustard therapy at present is indicated only when the process is so extensive and severe that roentgen ray therapy cannot be used. Perhaps we may expect in the future new chemicals related to nitrogen mustards that will produce more favorable results.

DR. ANTHONY C. CIPOLLARO: It is interesting to note that cases of mycosis fungoides respond to various types of ionizing radiations. This patient responded

to treatment with thorium X. If we were to treat the entire body with that preparation the cost might be prohibitive. Radioactive sodium therapy has given good results in the cases in which it has been used, but the systemic effect is deleterious. It has also been brought out that nitrogen mustard causes involution of some of the lesions, which later recur. In a few cases there has been remission after treatment with thorium X. When compared with the time-honored method of roentgen ray therapy, these newer methods do not give comparable results. Roentgenotherapy causes greater involution and for longer periods. I have had patients under treatment with roentgen rays for fifteen and twenty years and more, with excellent results.

DR. HOWARD FOX: I agree that the best treatment for this disease is roentgen irradiation. I should like to ask Dr. Cannon what Dr. Fordyce's experience was with administration of a combination of roentgen rays and arsenical preparations.

DR. A. BENSON CANNON: I have seen only 1 patient with a case of mycosis fungoides in the tumor stage who became cured. This patient, a woman about 35 years old, was treated by Dr. Fordyce some thirty years ago and has remained well to date. She had about three hundred nodules and tumors, a few the size of a grapefruit. All lesions disappeared on treatment with radiation and eight weekly injections of neoarsphenamine.

DR. GEORGE M. LEWIS: A patient presented at the New York Academy of Medicine two months ago had become roentgen ray fast and was in a critical condition. To our amazement, after only a few doses of antimony potassium tartrate there was involution of all the lesions except for a few small, infiltrated plaques. The response was nothing short of miraculous. Anyone who saw the patient could not help but be impressed with the possibility that this therapy is a specific at least in some cases. My associates and I have tried it in 4 cases since, in 1 with good results but in the others with no response. It is probably highly selective therapy, and we feel from our limited observation that it is most useful in the tumor stage, rather than sooner.

DR. GEORGE C. ANDREWS: I am glad the members take the view that my associates and I do, that it is better to hold off giving nitrogen mustard. We have had experience with that drug in other cases, and though the condition has cleared up for a few weeks the side reactions have been so bad that we think it wiser not to use it except in unusual instances. This patient was in a bad condition when we started giving antimony potassium tartrate. The results at first were marvelous. Then he manifested weakness and swelling of the legs and the electrocardiogram showed changes; consequently we stopped treatment, and the disease became worse again. Dr. Garb has seen this patient, and he prefers antimony potassium tartrate to stibanose® (the diethylamino-ethanol salt of sodium antimony gluconate) or stibophen, but there is probably not much difference in their effects. The results of thorium X therapy have been satisfactory. After only three or four treatments the skin cleared up nicely. I think we shall use it more extensively.

**Radiodermatitis with Multiple Epitheliomas.** Presented by DR. PAUL E. BECHET.

J. R., a woman aged 43, stated that many years ago she was given radiotherapy in epilating doses on her face and arms, at a commercial institution, for the relief of a moderate hypertrichosis. She now presents radiation sequelae of severe degree on her face and arms, with excoriated, scaly lesions suggestive of neurotic excoriations, and also a large number of epitheliomas on her face and arms. Therapeutic suggestions would be welcomed.

DISCUSSION

DR. A. BENSON CANNON: I can see very little evidence of overiradiation in the patient's skin, and most of the wounds present are obviously traumatic, though a few are keloidal and others are only suggestive of epithelioma. I am inclined to consider the case as one of neurotic excoriations. Most epitheliomas occurring in roentgen ray burns are of the basal cell variety. My statistics show nine basal cell lesions to every squamous cell epithelioma. The more pronounced and deeper the radiation burn and the larger the growth, the more likely the epithelioma is to be the squamous cell variety.

DR. EUGENE F. TRAUB: This is another example of damage incurred from treatment at this institution. In this instance both the patient's face and arms were treated. There are a number of lesions present that seem beyond the area of exposure and certainly beyond the area of visible sequelae. The eruption seemed primarily inflammatory and in some areas was extremely superficial and atrophic. There was some pruritus. I believe the diagnosis of superficial disseminated lupus erythematosus should be considered, and this might explain the lesions in the outlying areas. Another possibility is that of lichen planus, which might account for much of the itching. The infiltrated lesions are definitely epitheliomas. While many have thought that areas of radiodermatitis invariably give rise to prickle cell epitheliomas, Dr. Cannon is quite correct in his observation that very often basal cell lesions develop in such areas—probably even more frequently than do prickle cell lesions. I believe it is probably commoner for one to see basal cell forms in areas of mild dermatitis, and prickle cell lesions where the radiodermatitis has been severe.

DR. PAUL E. BECHET: The case is interesting because of the fact that some of the epitheliomas occurred where there was no radiodermatitis, so that, while a number of them seemed to have developed as a result of the radiodermatitis, others did not. Because of the extensive radiodermatitis, roentgenotherapy was of questionable value.

**A Case for Diagnosis (Gumma?).** Presented by DR. OTIS FIELD JILLSON for DR. A. BENSON CANNON.

J. H., a man aged 35, born in the Dominican Republic, is presented from Vanderbilt Clinic with destruction of the nasal septum of nine months' duration. He first noted a purulent nasal discharge, which was found to be associated with an ulceration of the nasal septum. He was treated with sulfathiazole powder applied locally and penicillin administered intramuscularly for one month, but the destructive process continued.

The entire nasal septum has been destroyed. There is necrotic granulation tissue covering the floor of the nose and the surrounding skin. There is a purulent, foul-smelling nasal discharge. The remainder of the physical examination showed an essentially normal condition.

A complete blood count showed 10.7 Gm. of hemoglobin, 3,800,000 red blood cells and a normal differential count except for an eosinophil count of 8 per cent. The urine was normal except that it contained albumin (1 plus). Cultures of the nasal secretions showed only Escherichia coli. Examinations revealed no anaerobic organisms or fungi. Roentgenograms of the nasal sinuses showed normal conditions except for cloudy right ethmoid cells and antrums. Roentgenograms of the lungs revealed only soft shadows of both apexes. No active lesions were observed. Findings in roentgenograms of the heart and great vessels were within normal limits. The examination of the spinal fluid showed a negative Wassermann reac-

tion, a normal colloidal gold curve and no increase in the amount of protein or cells. Kline and Wassermann reactions of the blood were negative on two occasions. Dark field examinations of the granulomatous lesion gave negative results. The reaction to tuberculin was negative in a dilution of 1 : 1,000. Smears showed no leishmanias.

Biopsy showed tissue covered with epidermis, which was necrotic and ulcerated over one half of the section. Numerous deep hair follicles were seen, surrounded by large, deeply seated sebaceous glands. Hyperkeratosis extended deeply into these follicles. The rete was moderately acanthotic and edematous. In the region where hair follicles and sebaceous glands were plentiful, many striated muscle fibers were noted which appeared to be undergoing degenerative changes and were surrounded by areas of edema and round cell infiltration. Degenerated nerve fibrils and small vessels whose walls were undergoing degenerative changes could be seen in the same region. Underlying the area of epithelial necrosis and ulceration there was a rather massive granuloma composed of lymphocytes, epithelioid cells and young fibroblasts. Occasional large, pale, vacuolated cells, possibly tissue monocytes, were noted. Several cells of this type showed mitotic figures. Nothing was seen to suggest rhinoscleroma, paracoccidioidal granuloma, leprosy, yaws, epithelioma or syphilis. The pathologic changes consisted essentially of a granuloma at the edge of an ulcer. Recut sections failed to provide additional information. Sections have been ordered to be stained by the Warthin-Starry and Giemsa methods, and observations will be reported later. The diagnosis was infectious granuloma with ulcer.

While in Presbyterian Hospital the patient has received 1,000,000 units of penicillin daily for a total of 24,000,000 units, roentgen ray treatment (1,200 r) confined to the nasal region, and a total of 56 Gm. of sulfadiazine. There has been definite improvement.

DISCUSSION

Dr. Earl D. Osborne, Buffalo (by invitation): My impression is that the condition is syphilis. In spite of the negative serologic reaction, I believe that type of involvement is best explained by syphilis. The upper lip now shows a resolving, healing infiltrate which would best fit in with the tertiary stage of that disease.

Dr. Maurice J. Costello: I should suggest the possibility of destruction of the nose by microaerophilic hemolytic streptococci. I presented a patient with a picture not unlike this before the Section on Dermatology and Syphilology of the American Medical Association. I think anaerobic studies and a trial of treatment with zinc peroxide are indicated.

Dr. Henry E. Michelson, Minneapolis (by invitation): I always hesitate to accept a diagnosis of syphilis when the serologic reaction is consistently negative. I have seen very few cases of active syphilis in which there was a negative reaction. Having reached a therapeutic standstill with this patient, one should consider giving streptomycin because many germs of the nose and throat are susceptible to that drug.

Dr. Donald M. Pillsbury, Philadelphia (by invitation): While it is of course possible for this patient to have syphilis and a negative reaction to serologic tests for the disease, this situation would be very unusual in syphilis involving the nasal septum, according to my experience. The collateral evidence for syphilis in this patient is likewise unconvincing. This case is representative of a group of infections involving the center of the face, in which the exact cause and the eventual prognosis are difficult to determine. The destructive course of such lesions is

sometimes surprising and unexpected. I recall in particular a pilot in England during World War II who, after a slight injury to the face, acquired an invasive infection which resisted all types of chemotherapy and antibiotic therapy, involved all the sinuses and finally caused death. The present case falls into the same group, but apparently the process is gradually slowing down and the secondary infection is under control. I should like to ask whether this patient is being treated as for syphilis and, if so, whether any special benefits have been noted from administration of large amounts of penicillin, such as 1,000,000 units daily. It seems probable that a considerable proportion of the drug is being excreted without having exerted significant effect.

DR. A. BENSON CANNON: I agree with Drs. Michelson and Pillsbury that this case is far from being proved gumma. It was the history of insufficient treatment for syphilis, the patient's youth, the short duration and rapid destruction that caused us to think first of syphilis, but all reactions to serologic tests have been negative, and the patient has failed to show improvement on antisyphilitic therapy. My associates and I have had several cases with lesions similar to this, causing extensive destruction of the nose, but in each instance the reactions to serologic tests were strongly positive even though the condition responded very slowly to antisyphilitic therapy. Dr. Dennie reported a similar case before the American Dermatological Association at Colorado Springs, Colo., several years ago, of a patient with a strongly positive Wassermann reaction who finally died despite much treatment for syphilis. Dr. Dennie expressed the belief that the case was one of vasculitis.

**Pityriasis Rubra Pilaris.** Presented by DR. CHARLES F. POST for DR. GEORGE C. ANDREWS.

A. O., a man aged 44, of Hungarian extraction, is presented from Presbyterian Hospital complaining of thickening of the skin of the palms and generalized itching and scaling of the skin, of one year's duration.

For three and one-half years before the onset of the present eruption the patient operated a die machine. Copper wire was drawn to the desired diameter while being kept immersed in a cutting oil. The patient's hands and arms were constantly wet with this solution. In February 1947 the patient noted thickening of the palms and an erythematous eruption of the forearm, followed by pruritus and desquamation of the temporal region of the scalp. Within two months the face, neck and then the rest of the body were involved in an erythematous, dry, scaly eruption which has persisted with little change for the past ten months. Treatment by his physician consisted of emollient preparations and four roentgen ray exposures, given to the palms and forearms. In August 1947 he received potassium arsenite solution, beginning with 6 drops a day and increasing by 1 drop daily until 15 was reached, and then going back to 6 drops, in a total of eighteen days. The diet has apparently been adequate. No one in the family has had a similar eruption.

There was a generalized exfoliative erythroderma when the patient was admitted to the Presbyterian Hospital on Jan. 9, 1948. The palms and soles showed greatly thickened, devitalized skin, with fissures in the creases of the palms. The finger nails and toe nails were thickened and lusterless. There was moderate lichenification, most pronounced on the arms and legs. Scattered over the trunk and shoulders were a dozen or more areas of apparently normal skin 0.5 to 1 cm. in diameter. The lymph nodes in the axillas and inguinal regions were enlarged, freely movable, discrete and nontender. There was a profuse purulent discharge from the left ear.

The white blood cell count was 11,400, with 51 polymorphonuclear leukocytes, 42 lymphocytes, 3 basophils and 4 eosinophils. The blood contained no free carotene, but the vitamin A level was 100 micrograms per hundred cubic centimeters. The arsenic content was 0.09 mg. per hundred grams of dry blood, and a twenty-four hour specimen of urine contained 0.06 mg.

Biopsy of the skin showed hyperkeratosis and parakeratosis. The follicles and sweat gland orifices were densely packed with keratin plugs in whorl formations. There was a moderate degree of acanthosis. The nuclei of the basal layer showed numerous normal mitotic figures. The blood vessels of the corium were dilated, and a perivascular lymphocytic infiltrate was present. An inflammatory reaction was also seen around the pilosebaceous apparatus. The sweat glands were distorted and atrophic. These changes were considered compatible with a diagnosis of pityriasis rubra pilaris. Biopsy of a lymph node showed changes of dermatopathic origin.

Chemical analysis of the lubricating oil showed that it had a $p_H$ of 7.8 and an arsenic content of less than 1 microgram per hundred cubic centimeters.

The patient was given 150,000 units of vitamin A daily, was placed on a high calory diet and had frequent application of cottonseed oil to the skin. On the sixteenth hospital day intramuscular injection of BAL in oil (a solution of 2,3-dimercaptopropanol, 10 per cent, in peanut oil, containing benzyl benzoate, 20 per cent) was instituted in doses of 4.5 cc. daily for the first two days and then in doses of 3 cc. daily, for a total of nine days. At this time the arsenic content of the blood was 0.15 mg. per hundred grams of dry blood, and a twenty-four hour specimen of urine showed 0.14 mg.

The patient was discharged, with considerable improvement in his condition, and he has continued to show improvement.

### DISCUSSION

DR. HOWARD FOX: I doubt the diagnosis of pityriasis rubra pilaris in this case because the patient gives no history of having normal white areas of skin with little keratotic papules in the neighborhood. He has no keratotic plugs on the backs of the last two phalanges of the fingers. He has no appreciable scaling of the scalp and not much keratosis of the palms. I see nothing at present on which a positive diagnosis of this disease can be based.

DR. GEORGE M. MACKEE: I agree with Dr. Fox. I should find it difficult to establish a definite diagnosis of pityriasis rubra pilaris. If I were asked to make a clinical diagnosis I should say universal erythroderma. This disease sometimes results in mycosis fungoides or one of the members of that group of disorders. The present condition might even be universal erythroderma occurring in neurodermatitis disseminata.

DR. GEORGE C. ANDREWS: The patient should have been presented as having pityriasis rubra pilaris 95 per cent cured. His condition has changed completely in the last three or four weeks. When he was first seen, there were many areas of normal skin. That was one of the outstanding features. He had a universal erythroderma with isolated areas of perfectly normal skin the size of a quarter to that of a half dollar. He did have great thickening of the palms and soles. The eruption had a yellowish pink color. The histologic picture is typical. The patient started to show improvement in the hospital. After the improvement began, in spite of the fact that the results of arsenic determinations were almost normal, the compensation department more or less insisted that BAL be used. It was, and the patient's condition is very much better.

**A Case for Diagnosis (Erythema Multiforme Bullosum? Mycosis Fungoides?).** Presented by DR. EDWARD BARR for DR. J. LOWRY MILLER.

B. B., a man aged 73, is presented from New York City Hospital with a generalized dermatitis of three months' duration. The patient arrived in the United States one and one-half years ago from Poland, where he had been imprisoned for four years. He was well until three months before admission, when there developed on the volar aspect of the right wrist a dime-sized, erythematous, pruritic lesion covered with pinhead-sized vesicles. Within a week the lesions had spread to the entire right upper extremity and had become intensely pruritic, erythematous, confluent plaques. After another week the left upper extremity became similarly involved, and then both lower extremities were. Several days later, discrete, erythematous lesions 2.5 cm. in diameter appeared on the abdomen, soon developing into generalized pruritic plaques. During this entire episode there were no chills or fever. There was no history of drugs taken for catharsis, headaches or nervous disorders or as tonics.

On the patient's admission, the greater part of the body surface was covered by a wide variety of lesions, ranging from erythematous, indurated, confluent, plaque-like lesions on the forehead, upper extremities, back and lower extremities, to discrete, erythematous, annular lesions 2.5 cm. in diameter on the abdomen and anterior portion of the thorax. The periphery of both the confluent and the discrete lesions was indurated, and central clearing was seen. The lesions on the back and upper extremities appeared to have serpiginous borders. Occasional bullae were noted on the ears and upper extremities. No hemorrhagic centers were observed. However, there were normal areas of skin located centrally in the discrete areas on the abdomen. The bullae contained clear fluid. The eyelids were edematous. There were no lesions in the oral cavity or the nares or on the penis, and the palms, soles and scalp were likewise free.

Examination otherwise showed normal conditions except for inspiratory and expiratory wheezes in the chest bilaterally and rhonchi and rales in the bases of both lungs. There was no significant lymphadenopathy on admission.

The Mazzini reaction of the blood was negative. Roentgenograms of the chest showed prominent bronchovascular markings without definite evidence of specific lesions. The results of urinalysis were normal. The blood count showed 15 Gm. of hemoglobin and 23,000 leukocytes, with 44 polymorphonuclear leukocytes, 26 lymphocytes, 26 eosinophils, 2 myelocytes and 2 monocytes. The erythrocyte sedimentation time was 1 hour plus (Cutler method).

While the patient was in the hospital there developed a cellulitis of the left lower extremity, with a temperature of 100.2 F. and generalized painful lymphadenopathy. The lesions on the back have been regressing without treatment. Many vesicles and bullae have appeared within the last three days.

Treatment has consisted of the application of wet saline dressings with elevation of the left leg and the administration of penicillin, 50,000 units every three hours, started on February 15.

DISCUSSION

DR. HENRY E. MICHELSON, Minneapolis (by invitation): After considering all the possibilities which quickly came to mind, I believe this condition to be mycosis fungoides. It is too severe and long-lasting for erythema multiforme, and, even though bullae are present, it doesn't seem to be pemphigus vulgaris.

DR. DONALD M. PILLSBURY, Philadelphia (by invitation): I was struck with the amount of pyoderma. I do not believe it is a basic feature of the eruption.

but certainly it is obscuring the characteristic features of the underlying dermatosis. The clinical appearance is that of a streptoderma, and it is entirely possible that penicillin-resistant organisms are present. I should suggest a thorough trial of local antibacterial therapy, along with the administration of sulfonamide drugs by mouth. It has been my associates' and my experience that in chronic or acute secondary infections of various eruptions of the skin, 70 per cent alcohol is often the most useful single measure for keeping the contaminating bacterial flora in check. While it is true that raw and abraded areas sometimes will not tolerate this type of treatment, it is surprisingly nonirritating to most patients.

DR. EUGENE F. TRAUB: It seemed to me that a hemolytic organism, possibly the hemolytic staphylococcus, might produce this extremely peculiar reaction. Blood cultures or other investigations along this line might be of help.

DR. PAUL E. BECHET: I should be in favor of a diagnosis of mycosis fungoides. The configuration, the absolutely sharp line of demarcation and a certain amount of infiltration which is a little harder than the usual edematous infiltration of erythema multiforme all suggest mycosis fungoides. On the other hand, the lesions on the hand had the perfectly clear centers that are seen in erythema multiforme. The pustular appearance of a good many of the lesions, to my mind, is secondary. The man has severe pruritus with many pustules, which are common among laborers with dirty skins, and so I do not think the pustulation is a diagnostic factor.

DR. ANTHONY C. CIPOLLARO: I should like to go along with those who feel that the condition is mycosis fungoides, with perhaps a superimposed erythema multiforme. We must consider the history. The eruption is of only three months' duration, and during this period it spread rapidly over the body. Mycosis fungoides is a slowly developing disease. A therapeutic test with roentgen rays may be useful in differentiating that disease from others. This person has not been tested with roentgen rays, as I understand it, and it might be well to do so and see whether the eruption would respond. On the basis of one biopsy a diagnosis of mycosis fungoides cannot be made. I should suggest that another be performed.

DR. J. LOWRY MILLER: My associates and I had the same difficulty when we first viewed the patient, and at that time the infiltration of many lesions was more pronounced. Even without roentgen ray treatment many lesions have undergone involution. We purposely withheld roentgenotherapy in order to present the patient at this meeting.

**Sarcoidosis.** Presented by DR. CARL T. NELSON for DR. GERALD F. MACHACEK.

E. M., a Negro aged 32, presented from the Vanderbilt Clinic, was born in the British West Indies but came to this country twenty-nine years ago at the age of 3. He had had no cutaneous lesions prior to the onset of his present eruption. About three years ago annular, infiltrated lesions developed on the eyelids, nasal folds and the back of the neck. These were asymptomatic. Similar lesions gradually appeared on the cheeks, forehead, scalp, scrotum and legs, remained relatively constant in size and showed no tendency to disappear. There has been little or no change during the past year. The patient has felt remarkably well. He has noted transient painless enlargement of the cervical lymph nodes at times. There has been no swelling of the parotid or lacrimal glands, and he has had no ocular symptoms, chronic cough or swelling of the fingers. The patient has been seen in three local hospitals and in each was told that he had "a form of skin tuberculosis," but no treatment was instituted. Roentgenograms of the chest and hands allegedly showed normal conditions two years ago.

The skin shows a number of annular, infiltrated, plaquelike and papular lesions involving the eyelids, cheeks, neck, scalp, forehead, scrotum and legs. These

lesions range from 0.5 cm. to 6 cm. in diameter, and some of the larger ones are violaceous. Some, particularly on the legs, show scaling in the central portions. There are no other abnormalities except for enlarged, freely movable, nonpainful axillary and inguinal lymph nodes.

There was 13 Gm. of hemoglobin, and white blood cells numbered 6,650, with 47 polymorphonuclear leukocytes, 49 lymphocytes, 1 monocyte and 3 eosinophils. The Wassermann reaction of the blood was negative. Tests with old tuberculin in dilutions of 1:10,000, 1:1,000 and 1:100 had negative reactions. The test for the Kveim reaction was performed on Feb. 9, 1948.

The following further observations were made of the blood: 11.2 mg. of calcium, 21.0 mg. of nonprotein nitrogen, 4.2 Gm. of albumin and 4.2 Gm. of globulin per hundred cubic centimeters. There were 5.8 Bodansky units of alkaline phosphatase and 179.0 mg. of cholesterol per hundred cubic centimeters.

Roentgenograms of the chest showed some parenchymal infiltration and enlargement of the hilar lymph nodes suggestive of sarcoidosis. Roentgenograms of the hands showed some rarefaction in the terminal phalanx of the left fifth finger, but no other abnormalities.

*Biopsy*—Neck: The corium was seen to be filled with masses of epithelioid cells. In places these appeared as small aggregations; in others they were diffusely distributed. There were a number of Langhans' giant cells and many large, pale-staining giant cells containing irregularly distributed nuclei. A few clear cells were found in which the cytoplasm appeared somewhat foamy. Surrounding these cell masses there was a moderate inflammatory reaction, with some proliferation of fibrous tissue. Around the masses the collagen was edematous and hyalinized, and in the neighborhood of the coil glands there was a mild inflammatory infiltration of round cells with a few polymorphonuclear and plasma cells. Melanin and hemosiderin could be seen in the cutis. In some portions the giant cells and the large epithelioid cells contained vacuolated areas with irregular inclusions almost suggesting the possibility of a deep mycosis such as cryptococcosis. Sections stained by the Ziehl-Neelsen method showed no acid-fast organisms. The diagnosis was atypical sarcoidosis.

Leg: The dermis was widely infiltrated with epithelioid cells. Although well delimited aggregations of these cells occurred, the tendency toward a diffuse distribution was greater than that seen classically in sarcoidosis. A number of large giant cells of the Langhans type were noted, and in some areas necrobiosis of the collagen could be seen. In other portions a little necrosis of the type associated with some tuberculous granulomas was present. The corium contained considerable hemosiderin and showed widespread fibrosis and infiltration with round cells. This specimen showed more inflammation than the other tissues submitted from this patient. Ziehl-Neelsen stains failed to reveal any acid-fast organism. The diagnosis was atypical sarcoidosis.

### DISCUSSION

Dr. Henry E. Michelson, Minneapolis (by invitation): I think the diagnosis of sarcoidosis is correct. Having attended a committee meeting on the subject recently in Washington, I should like to say a few words in general. In the Army about 350 cases of sarcoidosis were discovered, and in about 20 necropsy was performed. The ratio of Negro patients to white persons was about 16 to 1. Geographic distribution seemed to be important. Many of these patients, especially Negroes, came from the southeastern Atlantic states. I was amazed to see the rather positive position that nondermatologists took, for example, listing the superficial lymph glands as first in order of involvement, the lungs as second, and then

the eyes, the skin and the bones. Glandular enlargement may come first in Negroes, but I do not believe that it does in white persons. I have seen few cases in white persons in which there were not cutaneous lesions. I must stress the polymorphic nature of cutaneous lesions as seen in the present patient.

Certainly microscopic corroboration is always necessary in order for one to make the diagnosis, but one must set rigid boundaries in making a microscopic diagnosis. Rich mentioned eosinophils being seen in early lesions. He also felt that the presence of Schaumann bodies in the giant cells ruled out tuberculosis, but the bodies were only found in 50 per cent of cases. Many pathologists are not so impressed with the presence of Schaumann bodies. If one makes three columns and thus compares tuberculosis (general) with sarcoidosis in white persons and in Negroes, one may be quite impressed with the similarities found between sarcoidosis in Negroes and tuberculosis. So, from the present weight of evidence, sarcoidosis in the Negro comes closer to tuberculosis than to any other disease. The subject is a big one and needs much study.

DR. MAURICE J. COSTELLO: Does Dr. Michelson think that the favorable response of some of these patients to calciferol is an indication of a tuberculous causation?

DR. HENRY E. MICHELSON, Minneapolis (by invitation): Calciferol is not a specific. It cannot be likened to arsenic or penicillin in the treatment of syphilis. Even in the treatment of lupus vulgaris, the one disease in which the results have been the best, it does not have perfect results. One author compared the use of calciferol in the therapy of lupus vulgaris to that of iodides in treatment of tertiary syphilis. The lesions are controlled, but the disease is not cured. Nitrogen mustard has been used successfully in treatment of sarcoidosis.

**Chronic Disseminate Discoid Lupus Erythematosus with Poikiloderma-like Changes.** Presented by DR. BENJAMIN J. CHESTER for DR. J. GARDNER HOPKINS.

S. H., a Canadian-born man aged 25, is presented from Vanderbilt Clinic with an eruption on the face, scalp, trunk and upper extremities, of twenty-one years' duration. When the patient was aged 4, after a day at the beach, his mother noticed a red spot on one cheek, which persisted. He was taken to a local hospital and given roentgen therapy and ultraviolet irradiation, after which the eruption became generalized. Two years of a gold treatment gave little benefit. At the age of 10 the patient received a bismuth preparation intramuscularly, with some improvement. He also began to avoid sunlight, which made the eruption worse. For the next eight years he attended various clinics and received gold and bismuth compounds, with some benefit at first. Cervical adenitis, which required incision and drainage, developed at the age of 8 or 10.

The patient was first seen at Vanderbilt Clinic and admitted to Presbyterian Hospital in 1940, at the age of 18. The lesions were essentially like those of the present eruption except that the lower extremities were also involved. Enlarged lymph nodes were noted in the cervical, axillary and inguinal regions. The liver extended 1 fingerbreadth below the costal margin. The patient's temperature varied between 98 and 100.6 F. during his hospital stay. He was given intramuscular liver therapy, with some benefit at first. From March 1942 until January 1948, when he was again seen in this clinic, he received no medical attention. There has been no great change in the skin in the past six years; however, the patient noticed that sunlight and even sunburn no longer aggravated the lesions. He has worked in the engine room of a ship in temperatures over 100 F. with no

apparent effect on the skin. His general health has been good; he has no muscular weakness but tires more easily than normal. Seven months ago he abraded the skin of his back. The lesion crusted but did not heal; after biopsy it healed except for a small crust.

The scalp shows some scaling and a small area of atrophy at the vertex. The hair is fine and moderately thinned. There are erythematous plaques with thin, silvery scales over the forehead, nose, malar regions, lips, chin and neck. The lesions are slightly raised and do not show follicular pluggings. The skin is smooth and atrophic over the nose, with yellowish milia-like lesions about the hair follicles. The lips show wrinkling and silvery scales. There are many areas of telangiectasia. The trunk shows erythematous plaques with large, mica-like, silvery scales merging with areas showing a network of erythema, which represents dilated blood vessels. On diascopic pressure the vessels are obliterated, leaving a network of pigmentation. The upper extremities show the same type of plaques except that those on the lower portions are less erythematous and scaly.

The erythrocyte sedimentation rates were within normal limits in 1940 and 1948. Roentgenograms of the chest showed calcification in both hilar regions. The amount of serum protein and the albumin-globulin ratios were normal; the amounts of serum calcium, phosphorus, phosphatase, nonprotein nitrogen and cholesterol and of plasma vitamin C were all within normal limits. The reactions to tests with tuberculin were negative in dilutions of 1:1,000,000 and 1:100,000. The patient showed sensitivity to ultraviolet radiation at about 3,000 angstrom units in 1940. The twenty-four hour specimen of urine showed 177 micrograms of coproporphyrin in 1940, and 40 micrograms in 1948. The cephalin flocculation test gave a 2 plus reading in 1948.

In July 1940 a biopsy specimen taken from the right lower thoracic region posteriorly was reported as showing lupus erythematosus. In September 1941 from a specimen taken from the skin and pectoralis major muscle the diagnosis of scleroderma (type?) of the mammary region was made; the muscle was normal. In 1948 a biopsy specimen from the skin of the chest showed lupus erythematosus; one from the crusted lesion on the back was diagnosed as scar, granulation tissue.

DISCUSSION

DR. HENRY E. MICHELSON, Minneapolis (by invitation): I was particularly interested in the microscopic sections, for I believe one must stress the need of focusing on the pathologic changes of the corium in lupus erythematosus. The epidermal changes are secondary. Edema, connective tissue changes, infiltrate, even free red blood corpuscles, and then the secondary epidermal atrophy, follicular dilatation and plug formation follow. In the slide of the specimen from the skin of the chest, edema was the striking feature.

**Ulcus Vulvae Acutum.** Presented by DR. A. BENSON CANNON.

R. M., a 31 year old mother of one son, was previously presented before the New York Dermatological Society on Dec. 16, 1947. She was admitted to the Presbyterian Hospital the following day.

The patient has enjoyed good general health and has had no serious illnesses. Two years ago there was an acute onset of a griplike illness, associated with painful small blisters and ulcers on the tongue, lips and gums. This attack subsided spontaneously in several weeks. Since then, at intervals of several months, recurrences have appeared. About one year ago lesions developed on the genitalia as well as on the oral surfaces. No ocular symptoms were present at any time.

nor was there any fever, loss of weight or constitutional symptoms. During the past year red, tender papules have appeared on the legs. This eruption has not been associated with the outbreaks of ulceration.

Examination on admission showed normal conditions except for many small, superficial and deep ulcerations of the tongue, lips, hard palate and vulva; a single tender nodule on the anterior aspect of the left leg, and a uterus enlarged to the umbilicus.

Attempts to demonstrate a virus in the lesions were unsuccessful. Voided urine showed occasional white blood cells and a trace of albumin. Blood studies showed normal conditions except for an amount of hemoglobin of 10.6 Gm. Serologic tests for syphilis gave negative reactions. Culture of material from the lip produced Staphylococcus albus, green-producing streptococci and no anaerobic organisms. Culture of material from the vulva grew green-producing streptococci and no anaerobic organisms. Repeated blood cultures were sterile. Smears for Vincent's organism were negative. The nonprotein nitrogen was 28 mg., the blood sugar, 93 mg., and the protein, 6.3 Gm., per hundred cubic centimeters.

Biopsy of a nodule from the leg on December 18 showed edema of the corium and considerable perivascular infiltration of small round cells, changes in the walls of the blood vessels and areas of fat replacement atrophy. The histologic diagnosis was erythema nodosum.

Biopsy of a lesion of the vulva on January 6 showed a deep ulcer surrounded by a pronounced inflammatory reaction. Numerous capillaries were present. Some blood vessels showed obliterative changes. The histologic diagnosis was chronic ulcer with granuloma and obliterative endarteritis.

The patient has received a variety of treatments, with the following items: snake venom, transfusions, repeated doses of smallpox vaccine, tripelennamine pyribenzamine,® roentgen radiation in contact therapy to lesions of the vulva (1,000 r, twice) and bacitracin ointment. The lesions are now in remission.

NOTE.—The patient had remained completely well to the time of the last examination, in September, 1948.

DISCUSSION

DR. DONALD M. PILLSBURY, Philadelphia (by invitation): During the past year Dr. Harvey Blank of the Hospital of the University of Pennsylvania has been studying a series of patients with chronic ulcerative lesions of the mouth, and a few patients with lesions in both the mouth and vagina, in an effort to isolate a causative virus or other infectious agent. He has not found a virus in any patient, and there has been no regularity of the bacteriologic findings. These studies have been complete and thorough.

**Granuloma Annulare.** Presented by DR. MARVIN E. MCRAE for DR. GERALD F. MACHACEK.

J. N., a housewife aged 38, is presented from Vanderbilt Clinic with an eruption on the back of the neck and shoulders, of seven months' duration. In August 1947 pruritus developed on the back of the neck and the shoulders. The patient noticed that a roughly triangular area of skin, extending from the hairline at the back of her neck to the axillas, was reddened and covered with small papules of pinhead size or larger. She attributed this condition to overexposure to sunshine and applied calamine lotion containing phenol. The area slowly decreased in size until it was about 4 cm. in diameter, located at the base of the neck near

the midline. By the end of the following month it looked like a miniature of the present lesion. It then began to enlarge by peripheral extension, and the center cleared. Itching at times was moderately severe.

In 1943, while the patient was being treated for dermatitis venenata, Candida albicans was cultured from her toe nails, and it was noted that she had small psoriasiform lesions on her legs.

There is no family history of tuberculosis.

There is a large, reddened, roughly annular eruption on the cervicothoracic region of the back. The purplish red area is made up of separate and confluent, small, firm, deep-seated, flat-topped nodules. The wall varies in width from 1 to 4 cm. and is elevated 1 to 3 mm. above the normal cutaneous surface. The margin is interrupted in places, with the production of roughly crescentic patterns. The crescents are so arranged that they produce an incomplete oval approximately 9 by 15 cm. in diameter. The cleared center shows hyperpigmentation but no atrophy.

The Wassermann reaction of the blood was negative. Urinalysis showed albumin (1 plus), no sugar, 4 to 8 white blood cells and an occasional red blood cell. A complete blood count was normal. A roentgenogram of the chest showed no pathologic findings. The reaction to the tests with tuberculin was positive in a dilution of 1 : 10,000 and negative at 1 : 100,000. Examinations of the lesions for fungi were negative.

The first sections studied showed primarily a perivascular infiltrate and only minimal necrobiosis. These factors, together with a certain degree of mural degeneration of vessels, suggested erythema elevatum diutinum. On later sections the more typical picture of granuloma annulare was found, illustrating the fact that time is required for the full evolution of characteristic pathologic changes. The epidermis showed a mild, spotty parakeratosis. In some areas there was slight acanthosis, and in others the epidermis was somewhat flattened. There was intercellular and intracellular edema. The edema was more pronounced in the cutis, where small areas of coagulation necrosis could be seen, surrounded by irregular radiating arms of infiltration. The marginal bands of necrotic collagen appeared somewhat hyalinized, and within these areas could be seen collections of nuclear fragments. The infiltrate was composed of linear strands of epithelioid cells and numerous lymphocytes, with a few leukocytes and an occasional plasma cell. Throughout the cutis there was a perivascular infiltrate of round cells, and the vessels showed mild mural degeneration. In one area of necrobiosis there was seen a sharply demarcated area of hyaline degeneration of collagen suggestive of a Russell body. The diagnosis was granuloma annulare.

The patient has had 500 r of unfiltered roentgen rays given to the lesion. Itching has been controlled by tripelennamine.

**A Case for Diagnosis (Familial Benign Chronic Pemphigus? Keratosis Follicularis? Pemphigus Erythematosus?).** Presented by DR. CHARLES SHEARD JR. for DR. GEORGE C. ANDREWS.

A. M., an American man of Russian Jewish descent aged 55, is presented from the Vanderbilt Clinic with a dermatitis involving the armpits and trunk, of six months' duration.

The patient was in his usual state of good health until July 1947, at which time an irritation of the skin of the right axilla appeared, without apparent precipitating factors. After applying zonite® (a solution of sodium hypochlorite), without relief for two weeks, he consulted a physician, who prescribed a salve which also failed

to help. There was moderate itching, and the patient noticed that friction from his shirt in the area would cause the skin to rub off. Four roentgen treatments were given and various salves were applied, without effect. In November irritation of the skin of the left axilla appeared. A biopsy specimen from the right axilla was reported by Dr. Weidman as having a picture consistent with chronic benign familial pemphigus and similar to keratosis follicularis.

In December a red macular eruption appeared on the chest and then on the back. At no time did the patient see any bullae or vesicles, though his wife spoke of "pus blisters." He remembers that the eruption consisted of several coin-sized, round erosions with crusts and that it itched. After a bout of fever he was given penicillin, which produced a generalized, macular, pruritic eruption. He was then admitted to the Presbyterian Hospital. No one in his family has had cutaneous trouble.

Scattered over the midportions of the chest and back there are many round, superficially eroded areas varying in size from 3 mm. to 3 cm., with some crusting. There are tags of epidermis at the fringe of these erosions, giving the appearance of numbers of shallow ulcers, possibly representing the bases of ruptured blisters. The surrounding skin is normal. There are no visible blisters, and the skin is tough and resilient and cannot be rubbed off with the finger. The axillas show similar erosions of the epidermis but with a larger area included, with occasional deep fissures. There are scars from the removal of tissue for biopsy in the right axilla and on the left side of the chest. There is some scaling between the toes. A small (2 mm.) round, shallow ulcer is seen on the hard palate. General physical examination discloses no obvious disease beyond congenital deaf-mutism and moderate pyorrhea.

Serologic reaction of the blood (Kline) was negative, and a complete blood count was normal. The vitamin C level of the plasma was normal. The cephalin flocculation reaction was 2 plus. A culture of the skin from the right axilla grew hemolytic Staphylococcus aureus and aerobacter organisms. Scrapings from the toe webs were positive for fungi, but scrapings from the lesions on the trunk were negative.

Biopsy of a specimen from the chest showed slight parakeratosis with occasional acanthosis and formation of lacunas immediately above the basal cell region. There was some edema and lymphocytic infiltration, especially beneath an area where the epidermis had ulcerated. There was a proliferative tendency around the hair follicles.

A biopsy specimen from the right axilla showed extreme hyperkeratosis, with the surface delicately verrucous. There was pronounced acanthosis, with a tendency to proliferate into the wall of a sweat duct. Lacunas appeared at a level intermediate between the basal and prickle cells. Corps ronds were not seen. The apocrine glands were examined for keratinization extending into them from the ducts, but this was not found. Dr. Weidman's conclusions were that this disease was rather similar to familial benign chronic pemphigus (the Hailey-Hailey syndrome), though keratosis follicularis (Darier's disease) and pemphigus were less likely possibilities.

Biopsy of a specimen from the back revealed a small vesicle the size of a low power field in the prickle cell layer. Dr. Machacek's conclusion was that this observation was compatible with pemphigus vulgaris or chronic benign familial pemphigus.

Boric acid ointment, 10 per cent, was applied to the chest and axillas, with nothing to the back. Carbarsone, 100 mg. daily, was given for three days, 250 mg. for five days and 750 mg. for seven days, without change in the patient's condition.

DISCUSSION

DR. HENRY E. MICHELSON, Minneapolis (by invitation): I think that this case is one of familial benign chronic pemphigus. I formerly missed this diagnosis often. I now believe that the microscope will verify the clinical diagnosis and is quite accurate. I also want to call attention to the successful use of sulfapyridine in treatment of such patients. It is almost a specific in some instances.

DR. EUGENE F. TRAUB: This case should be watched closely as there is a strong possibility that it might terminate as the ordinary variety of pemphigus.

DR. GEORGE C. ANDREWS: There is a tremendous infiltration of lymphocytes in the corium, which is not found in familial benign chronic pemphigus. The man has been under my observation since he first acquired the eruption. At the beginning I thought he had seborrheic dermatitis. The disorder cleared up, then recurred and finally became vegetative in the axillas. Then the patient began having lesions on the trunk and was sent to the hospital, after which real bullae developed. My associates and I took more biopsy specimens, and recently these have looked more like pemphigus, although the bullae in the epidermis were higher than usual. The course has been favorable. As a result of taking carbarsone the patient feels much better and is back at work and all lesions have disappeared. I am inclined to think that pemphigus vulgaris with negative lesions is developing.

**Chronic Lymphedema of the Face.** Presented by DR. JAMES T. HEARIN for DR. J. LOWRY MILLER.

N. W., a man aged 50, is presented from Vanderbilt Clinic with swelling about the eyes, of three years' duration. In 1944 it was called to the patient's attention that his speech was slurred. About a year later puffiness appeared around his left eye, and eleven months later the tissues about the right eye became involved. These lesions and the dysarthria have grown gradually worse. The involved skin has never been painful or pruritic, and there are no cutaneous lesions elsewhere. The patient also complains of progressive hoarseness during the day and progressive fatigue of the muscles of mastication during the course of a meal. He has recently begun to note occasional pedal edema. He had been under the observation of more than two hundred physicians before coming to the Vanderbilt Clinic. Those with whom we have corresponded agreed with our diagnosis and also could elicit no significant laboratory findings.

The patient's general health appears to be good. The lesions are confined to the face and are characterized by swelling, thickening and a dull reddish discoloration of the skin. There is a slight increase in cutaneous temperature at the involved area, and the tissue pits on pressure. The tongue appears slightly enlarged, and moderate dysarthria can be noted.

Serologic tests for syphilis gave negative reactions on several occasions. Numerous complete blood counts have been entirely normal. On one occasion in July 1947, the sedimentation rate was slightly elevated. Roentgenograms of the sinuses, skull and chest have been repeatedly normal. Neurologic examination gave no clue to the cause of the dysarthria. Biopsy of the skin and subcutaneous tissue on Sept. 5, 1947, showed considerable edema and a perivascular and perilymphatic inflammatory reaction characterized by infiltration of lymphocytes. Cultures of material from the skin on one occasion revealed staphylococci and pneumococci. The results of urinalysis were normal, and determinations of serum protein and nonprotein nitrogen did not give remarkable results.

Skin testing with both epidermal and inhalant allergens has had uniformly negative results. In skin tests with staphylotoxin and streptotoxin there were negative results on both delayed and immediate examination. A skin test for trichinosis had equivocal results.

Prolonged courses of treatment with sulfadiazine, diphenhydramine (benadryl®) and penicillin, the latter also given subcutaneously into the involved area, produced no benefit. Local implantation of a nylon thread to stimulate drainage of the lymph was without effect. Thyroid extract, 4 grains (0.25 Gm.) daily, produced no benefit.

DISCUSSION

DR. ANTHONY C. CIPOLLARO: The cause of chronic lymphedema of the face is seldom ascertained, and this case proves that fact again. From the standpoint of therapy, I wonder whether something couldn't be done with plastic surgery. It would be worth while consulting a plastic surgeon in regard to removing the defects about the eyes. I also wonder if roentgen ray therapy might not be of some value. There is sufficient evidence, I think, to indicate that, if conservative doses are used, there should be no danger to the eyes. The papers by Jones and Alden proved that the eyes tolerate roentgen radiation as well as does the skin. I should be inclined to use roentgen ray therapy in cases of this sort.

DR. HOWARD FOX: With present knowledge, I think nothing can be done to help the patient.

DR. J. GARDNER HOPKINS: I don't think anybody would suggest treatment with a great deal of optimism. The majority of cases of chronic lymphedema due to staphylococci and streptococci present a history of erysipelatous attacks, which the present case does not. However, neither the lack of such history nor the negative reactions to skin tests with the toxins of these cocci rule out the possibility that treatment with these agents might be helpful.

**Herpes Zoster with Facial Paralysis.** Presented by DR. MEYER SLATKIN for DR. J. LOWRY MILLER.

F. G., a woman aged 68, is presented from City Hospital with a painful eruption and paralysis of the right side of the face and ear, of twelve days' duration.

Until October 1947, the patient's only illnesses had been hypertension and "rheumatism." At that time a lump was found in the right breast, a diagnosis of carcinoma was made and a radical mastectomy was performed at Memorial Hospital on October 12. In December the patient was given daily roentgen therapy to the operative site, right axilla, right side of the neck and back, for a total of fourteen treatments. The patient felt well until Feb. 12, 1948, when severe pains developed in the right cheek, the right ear and all the right upper and lower teeth. The following day she awoke to find the right side of the face numb and paralyzed, with slight diminution in hearing in the right ear and a vesicular rash on the chin and right side of the lower lip.

There are erythematous, vesicular and crusted lesions of the right ear (exclusive of the canal), the right cheek, the right mandibular area and the chin, stopping at the midline; paresis and paralysis of the muscles of the right side of the face and anesthesia of the right half of the anterior part of the tongue, and hyperpigmentation of the skin of the right side of the neck, the right axilla and the chest. A healed radical mastectomy scar is present. The oral hygiene is bad, with advanced periodontoclasia and caries.

Examinations of the urine and the blood revealed no abnormalities.

DISCUSSION

DR. EARL D. OSBORNE, Buffalo (by invitation): I have seen 2 similar examples, 1 with herpes in the same location, resulting from metastatic carcinoma. That is a possibility in this case.

DR. MAURICE J. COSTELLO: My associates and I have seen 2 patients at Bellevue Hospital within three months with facial paralysis accompanying herpes zoster without pain, both cases involving the maxillary branch of the fifth cranial nerve. The paralysis occurred on the nineteenth day after the appearance of the eruption.

DR. DONALD M. PILLSBURY, Philadelphia (by invitation): Dr. Geoffrey Rake, working with material submitted from our virology laboratory at the Children's Hospital, has had no difficulty in demonstrating a characteristic virus from herpes zoster lesions, which is indistinguishable from the virus seen in varicella lesions. Under the electron microscope these are fairly large, cuboidal bodies which, as I recall, have a characteristic flattening of one corner and are pathognomonic. There is no question that ideas as to the absence of a virus in the lesions of herpes zoster must be revised.

DR. J. LOWRY MILLER: My associates and I thought this case was interesting because we have seen one other within the month, with paralysis of the sixth cranial nerve, associated with herpes zoster.

**Leprosy, Lepromatous Type.** Presented by DR. JOHN F. DALY for DR. A. BENSON CANNON.

D. T., a Puerto Rican man aged 45, is presented from New York City Hospital. He was born and lived for forty-three years in Puerto Rico. In December 1946 he emigrated to New York city. Three years before that, he noted that he repeatedly burned himself on the anterior aspect of the right leg without pain. In June 1947 small, symptomless "lumps" appeared on the medial aspect of the lower third of the right leg. Similar lesions then developed on the left leg, the forearms, arms, thorax and ears, together with a dusky, erythematous, maculopapular eruption in the same areas, except for the ears. The nodular lesions of the ears appeared last, about one month after the onset of the eruption. The patient had no known fever, but during the development of the eruption he noted intermittent aching pains in the ankles, knees, elbows and shoulders. Since the first month he has noted no increase in the process. On Jan. 7, 1948, he was admitted to the skin service of City Hospital. There is no history of cutaneous disease in members of the family or in close associates. His father died at the age of 107, and his mother is alive and well at 90. The wife and seven children are said to be in good health.

The finger nails and toe nails present fine, longitudinal striations. The spleen is palpable beneath the left costal margin. There is numbness of the right leg from midcalf to the ankle and of the left leg about the ankle. The patient distinguishes differences in temperature poorly below the right knee and over an oval area on the lateral surface of the left ankle. Sensitivity to pain is retained to a lower level on the right leg than is thermal sense. No sensory disturbances of the arms, face or body can be elicited.

The cutaneous lesions are of two types, the first being small, firm nodules of normal skin color and the second, notably on the arms, consisting of duskily erythematous maculopapules, merging into a diffuse infiltration of the cutaneous surface. The pinnas and lobes of the ears are studded with small nodular lesions from 1 mm. to 3 mm. in diameter. There is no alopecia of the eyebrows or lashes. The arms and forearms, particularly on their extensor aspects, present a dusky red appearance which extends over the backs of the hands to the proximal phalanges. The skin is thickened and shows many maculopapules of deeper red and of variable sizes. Over this region are scattered nodular lesions varying

from 1 to 5 mm. in diameter. On the posterior aspect of the thorax are scattered erythematous macular lesions, usually of oval shape. Small nodular lesions of normal color or of waxy appearance are seen in the lumbar region and on the anterior thoracic and abdominal walls. On the buttocks there are densely set, dull red, scaly, papular lesions. The thighs and legs present numerous bluish red, oval maculopapules, interspersed with small nodular lesions. The dorsa of the feet and both soles present nodular, scaling lesions.

The Wassermann reaction of the blood was 2 plus to both alcoholic and cholesterolized antigens. There was a 1 plus reaction to the Mazzini test, a plus-minus reaction to the Kahn test and a negative reaction to the Kolmer complement fixation test. Blood counts and the erythrocyte sedimentation rate weer normal. The reaction to tuberculin was negative in a dilution of 1 : 10,000. Nasal smears contained numerous acid-fast, rod-shaped forms. Roentgenograms of the chest, hands and feet revealed no abnormalities. The histamine test performed on a macular lesion on the back produced both wheal and flare. In the pilocarpine test, applied to a macular lesion, there was produced a slight bluish color just above the site of injection.

Biopsy specimens were removed from a papular lesion in the right scapular region and from a nodule on the external aspect of the left elbow. Scrapings from the surface of the nodular specimen revealed many acid-fast bacilli, which were decolorized in five minutes. The biopsy of the nodular lesion showed a portion of skin with a thin, pigmented epidermis. The rete pegs were flattened, and both papillary and reticular corium contained multiple discrete and coalescing nodules of a granulomatous character. The nodules were composed chiefly of connective tissue and epithelioid cells, with a sprinkling of lymphocytes and plasma cells. There were also large cells with clear cytoplasm and compressed, eccentrically placed nuclei, as well as large clear spaces without nuclei. An occasional nodule contained a multinucleated giant cell. The nodules were grouped chiefly about vessels and in the neighborhood of hair follicles, and many lay just beneath the compressed epidermis. The Ziehl-Neelsen stain revealed numerous acid-fast rods, many in clumps lying intracellularly as well as extracellularly in the nodules. There were many bacilli outside the nodular areas, and some appeared to be in the epidermis. The histologic diagnosis was leprosy.

On January 24, 0.1 cc. of lepromin was injected intradermally on the flexor surface of the right forearm. Readings at seven and fourteen days showed no reactions.

Diasone® (disodium formaldehyde sulfoxylate diaminodiphenylsulfone) has been administered orally once a day, starting with 2½ grains (0.315 Gm.) on January 27. On February 2 the dose was increased to 5 grains (0.30 Gm.) daily, and on February 10, to 10 grains (0.60 Gm.). It is planned for the dose to be increased to 15 grains (1.00 Gm.) daily and to be continued at this level for an indefinite period.

DISCUSSION

DR. HOWARD FOX: This man shows all the signs of lepromatous leprosy. There are bacilli in the nose and the nodular lesions of the skin. I cannot detect enlargement of the ulnar nerves, but firm pressure caused no pain whatever. The negative reaction to the lepromin test shows that the disease is of the lepromatous type.

DR. A. BENSON CANNON: I am classifying this case as one of diffuse nodular leprosy. There is no normal skin to be found. The patient is a "red man." One can recover lepra bacilli from almost any place.